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EXPERIMENTAL EVIDENCE OF DIRECT COMMUNICATIONS BETWEEN LYMPH NODES AND VEINS

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IN THIS REPORT, experiments are cited indicating that direct anatomic communications exist between lymph nodes and venous channels and that materials may enter the blood stream from a node without passing through efferent lymphatic ducts. This finding explains a number of phenomena not previously well understood.

Ordinarily, communications between the lymphatic and venous systems are by a series of efferent lymphatic channels which join to form either the thoracic, the right lymphatic, or the subclavian ducts. However, there are a number of observed phenomena to be described later, which can be explained only by assuming that other pathways exist which bypass or short-circuit these anatomic routes. Yoffey and Courtice, for example, present ample evidence of the presence of lymphaticovenous anastomoses which shunt lymph from efferent channels directly into veins prior to reaching the larger ducts. There seems to be little doubt that they exist.

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Glenn and associates have demonstrated that if a peripheral lymphatic channel, as in the left leg, is injected with dye the latter will appear in the blood even if the thoracic duct is tied and thereby occluded. It is considered that this occurs by way of accessory lymphaticovenous communications which, though normally present, ordinarily carry little or no lymph. Drinker (3) has similarly described and Yoffey and Courtice have confirmed the presence of accessory channels between the thoracic duct and the right lymphatic duct of dogs. These permit materials injected into the peripheral nodes of the ipsilateral side to enter the blood stream despite experimental occlusion of the thoracic duct. It is suggested that normally little or no lymph flows through such accessory channels. They become enlarged and activated, however, when the main channels are obstructed or the lymph flow and lymph pressures are greatly increased. Yoffey and Courtice point out that this phenomenon has been described in other experimental animals besides the dog, such as the common rat and, according to Silvester, in New World monkeys. Carlsten and Olin have demonstrated their

presence by roentgenographic studies of cats. Semein and Andrioshin have demonstrated direct connections in human cadavers between the venous system and the lymphatics of the thyroid gland, esophagus, and glottis. These occurred in 34 of 276 cadavers.

The entire subject of accessory lymphaticovenous communications is thoroughly reviewed by Rusznyak, Földi, and Szabo in their new text. These investigators conclude that although lymphaticovenous communications can be demonstrated in anatomic preparations they are functionally negligible under normal conditions. They do not deny, however, that these communications can become functional.

The presence of lymphaticovenous communications does not, however, explain all the observed phenomena reported in a variety of experiments by many investigators. Thus Drinker and associates (4) found positive blood cultures after the injection of bacteria into a popliteal lymph node of the dog although they had taken the precaution of tying the thoracic and right lymphatic duct and both subclavian veins.

Bunting and Huston showed that when the thoracic and right lymphatic ducts are occluded most of the lymphocytes disappear from the blood, but this removal is never complete, and significant numbers of lymphocytes persist in the blood. Unless some other route of communication apart from the well known major channels exists between the lymphatics and the blood stream, all lymphocytes should eventually disappear, but this is not the case.

Yoffey and Courtice point out that in proved experiments such as those of McMaster and Hudack, having to do with the formation of antibodies in lymph nodes, the basic assumption was that bacteria which reach a node do not travel further in the efferent lymph or through the medium of phagocytes. Yet bacteria were found free in capillaries just outside the capsule of the node. One would suspect, therefore, that a route, apart from the usual channels, exists from the lymph node to beyond it. Their findings could be explained by a direct pathway from a lymph node to the vascular bed. Some evidence for this route is found in the writings of Schulze who believed that the postcapillary veins of lymph nodes possess stomas which afford a direct communication between blood and lymph glands. This communication explained the means by which noxious substances leave the blood stream and enter the node, but Schulze did not use this concept to explain passage in the opposite direction. Yoffey and Courtice conjecture that if these stomas really exist movement might also occur in the reverse direction and micro-organisms might enter the blood capillaries from the node. This theory, of course, could apply as well to other substances such as cancer cells.

Kubik, as cited by Rusznyak and associates, conjectures upon the possibility of fluid absorption into blood vessels taking place from the node, citing the fact that arteries entering into them are conspicuously wide and form an extremely delicate and profuse network of capillaries in the area of the marginal sinuses. Each follicle is surrounded by a dense capillary reticulum. The capillaries are drained by exceptionally wide veins. The number of afferent lymphatics entering the node is moreover always in excess of that of the efferent vessels leaving it, and the sum of the cross sections of afferent vessels is always in excess of that of the efferent lymphatics. We believe that all these facts furnish fairly convincing proof for the existence of absorption of fluids in the lymph nodes.

Objections to this concept have been raised principally by Drinker (4). These objections relate to the difficulties involved in the retention of structural integrity of the lymph node under conditions in which blood can enter it through open capillaries with no propulsive force available which can empty it, such as occurs from contractions of the spleen. However, one must bear in mind that such a force does exist in the

peripheral lymphatics in the form of active motion of the muscles. This produces a higher interstitial pressure than the 50 millimeters of mercury used in Drinker's perfusion experiments. Furthermore, Drinker states that if blood capillaries or stomas in the node were open, then lymph collected from an afferent vessel ought to contain much less protein than that from the efferent side. This is not the case, protein concentrations in afferent and efferent lymph being identical.

Engeset injected the lymph nodes of rats with metallic mercury and studied the distribution by roentgenography. This investigator found that direct communications between lymph nodes and vessels were present in 9 of 27 animals but interpreted this finding as due to artefacts.

There would, therefore, seem to be a number of observations concerning communications between the lymphatics and the vascular system not fully explainable by previously reported facts. If direct communication between lymph nodes and the vascular system were to be actually demonstrated, many of these experimental and clinical observations could be satisfactorily explained and differences of opinion reconciled. Such a phenomenon has, of course, been suggested on the basis of conjecture by others apart from Schulze and Kubik, notably Rouvière and Vallette, but actual demonstrations of such communications have not previously been made.

In the course of other experiments and by serendipity, it has been our good fortune to have demonstrated in the living dog that such direct communications do exist between lymph nodes and veins. Whether this is true in the other mammalian species as well, including man, has not been proved, but, although some variation in degree very likely exists from one species to another, it would be surprising if so fundamental and basic a relationship were to be present in one species of mammal and not at all in others. This is particularly true when one examines the origin of the lymphatic system as enunciated by Sabin and realizes that lymphatic channels as well as the nodes arise from outbuddings of embryonic veins. There is, therefore, every reason to presume a close anatomic relationship between them.

Our observations concerning these communications resulted from other experiments having to do with surgical studies related to the lymphatics of the neck. These experiments required positive identification of the principal efferent channel leaving the cervical nodes, as well as the recognition of any aberrant or anomalous channels that may coincidentally exist. Several methods of identification were used, including the clinical method described by Weinberg consisting of the injections of dye into the nodes. This dye readily entered the efferent channels which were thereby easily identified. Even a small amount of discoloration of the adjacent tissues which became stained after the efferent channels were tied posed certain problems, and a number of other techniques for identification of the efferent channels were tried. One of these consisted of injections of saline into a lymph node immediately followed by the injection of air at the same site. It was believed that this technique would result in the escape of bubbles into the efferent lymphatic channels which could thus be identified and isolated.

This fortunate attempt not only adequately demonstrated the efferent lymphatics but also, in virtually every instance, made direct communications clearly visible between the lymph node and the immediately adjacent and easily observable veins of the area. Some of these communications left the capsule of the lymph gland to enter the general plexus of veins of the region. The demonstration of these direct communications followed the injection of 1 or 2 cubic centimeters of saline into the node followed immediately by the injection of air at the same site using only moderate digital pressure upon the syringe. The vascular channels in the area of the node immediately filled with bubbles which were easily visible in the

blood stream within veins emerging directly from the gland as well as in communicating veins and the principal regional veins of the neck. These bubbles were carried away by the venous flow and could be made to recur repeatedly by subsequent small degrees of digital pressure upon the plunger of the air-containing syringe, the needle of which had been inserted into the substance of the node. The amount of contamination of the blood by air was in direct quantitative relationship to the degree of digital pressure used upon the syringe. In many instances, the displacement of venous blood by air was so great that even the large veins of the area were emptied of all blood and became air-containing rather than blood-containing channels. It was almost as if air were being injected directly into the veins, but this was not the case. Slowly, as the pressure was lessened, blood returned to the veins which gradually filled.

At the same time, the efferent lymphatic channels emerging from the lower pole of the cervical node were filled with bubbles so that entrance of the air into the venous and efferent lymphatic channels took place simultaneously. Occasionally, filling of the veins took place without gross evidence of air having entered the efferent lymphatic ducts but, even on such occasions, the application of negative pressure by withdrawal of the plunger of the syringe indicated that the needle was in the substance of the node but not in a blood vessel. As a matter of fact, many attempts in dozens of specimens to demonstrate the needle lying within a vascular channel within the node rather than within the substance of the node itself failed to give evidence of this and not in any instance was there the slightest indication of blood having entered the lumen of the needle or extravasated into the substance of the gland.

There is no question but that the site of injection within the gland plays a role, since, if initial attempts to produce the entrance of air into the veins fails, small movements of the tip of the needle will succeed in demonstrating the phenomenon. This favorable site has not been positively identified but is probably the lymph sinus. No attempt has been made to determine the degree of pressure required for either the introduction of the saline or the subsequent injection of air, but these pressures have not been excessive and were less than that required for the ordinary clinical subcutaneous injection of 1 or 2 cubic centimeters of fluid. It is our impression that the pressure differential required for the exchange of fluids or air between the veins and the node is very small, often being far less than that required for the passive extrusion of fluids from the substance of the gland into the principal efferent duct.

It is not known whether these direct communications between the nodes and the veins are one-way channels, permitting only the escape of injected materials from the node into the vein, or are two-way, permitting passage in the reverse direction from the venous system into the node.

The anatomic relationship which permits the escape of materials from the lymph node into the adjacent veins is more or less easily destroyed. Thus, repeated use of the same node to demonstrate the phenomena described will ultimately result in failure of air to pass from the node into the vein, but the nature of this destruction has not been ascertained.

We have not attempted to learn if liquids alone without the subsequent injection of air enter the vein from the node. This is more difficult to establish than one might suspect. Saline or other liquids including dyes cannot, of course, be visually recognized within the blood stream as can bubbles of air. Even when radioactive materials are injected and are almost simultaneously found in the adjacent veins, one has not ruled out their entrance by way of the established principal lymphatic pathways such as the cervical lymphatic trunk, the thoracic duct, or other aberrant pathways. Contamination of the blood via these routes takes place very rapidly.

If air in sufficient quantities is injected into the nodes of the neck, the veins can become virtually filled with air, and movement in a direction opposite to the normal venous flow ultimately takes place. Thus, air displacing the blood from the internal jugular system can sometimes be seen to flow in a reverse direction, passing from caudal to cephalad, probably because of increased intravenous pressure within the mediastinum. When the pressure is released and the needle withdrawn from the node, the force of the heart beat is increased and a return of venous flow in a normal direction takes place. The air is then displaced by blood, and the venous system once again assumes a normal appearance.

In one experiment in which a Y-shaped pattern of veins existed, the principal limb of the Y being caudad, air from a lymph node entered one secondary limb of the Y and, having filled the principal limb, began a circular flow between the two divergent limbs as though the pressure in the single limb below were too great to admit the entrance of any additional air bubbles into it.

SUMMARY AND CONCLUSIONS

Injection of lymph nodes with saline and then with air has demonstrated in colored motion pictures that direct connections exist between lymph nodes and veins. Even with minimal pressure, substances can be made to enter the vascular system through these direct communications without having entered the efferent lymphatic ducts. The existence of direct passageways between lymph nodes and adjacent cervical veins has therefore been proved.

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ENZYMATIC HISTOCHEMICAL PATTERNS IN SURGICALLY RESECTED THYROID GLANDS

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MICROMORPHOLOGIC STUDIES based on changes in acinar pattern and in parenchymal cytology of the diseased thyroid with hematoxylin and eosin do not reflect faithfully the metabolic dysfunction of the gland.

To seek further correlation between parenchymal cellular metabolic activity and morphology and to determine metabolic patterns associated with drug therapy, we undertook to study surgically resected thyroid glands with a group of enzymatic histochemical techniques.

MATERIALS AND METHODS

A series of 32 surgically removed specimens, 23 including adenomatous colloid goiters, 7 glands with diffuse hyperplasia, and 2 microfollicular adenomas of the thyroid gland, were obtained immediately after elective surgical excision in the operating room. In conjunction with studies, routine gross and microscopic examination of tissues was performed. Frozen sections of fresh and neutral formalin-fixed tissues for a group of histochemical techniques were made. These techniques included: Nachlas and associates' succinic dehydrogenase and diphosphopyridine nucleotide diaphorase methods, Wachstein's glucose-6-phosphatase and adenosine triphosphatase methods, and the nonspecific esterase technique, all described by Pearse; the alkaline phosphatase and acid phosphatase methods, described by Gomori; and the hematoxylin and eosin technique. Three normal thyroids removed with radical neck dissections were used as controls.

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RESULTS

The normal enzyme distribution in the thyroid gland is summarized in Table I.

Succinic dehydrogenase. This enzyme was consistently found in the parenchymal epithelium. The mitochondria appeared as small dark bluish granules or rodlets. The stroma and vascular walls were not reactive. In the adenomatous colloid goiter, no significant difference from normal was observed. In treated hyperplastic glands in areas of persistent hyperplasia, there seemed to be a slight increase of enzyme activity in the acinar cells.

Diphosphopyridine nucleotide diaphorase. The epithelial enzymatic pattern was the same as that described for succinic dehydrogenase. Moreover, the stroma and the vascular walls stained moderately. In the case of the adenomatous colloid goiter, no remarkable alteration was observed. In hyperplastic gland and follicular adenoma, the enzyme activity appeared similar to that of succinic dehydrogenase.

In hyperplastic glands which had been treated with sodium iothiouracil (itrumil) or iodine, foci of hyperplasia still showed increased diphosphopyridine nucleotide diaphorase and succinic dehydrogenase activity. However, in a case of diffuse hyperplasia treated preoperatively with 3, 5, diodothyoacetic acid (diac), the epithelial cells, even though tall, columnar, and morphologically hyperactive, showed significant reduction in these enzyme activities.

Glucose-6-phosphatase. The acinar cells were consistently negative. With longer incubation periods, portions of the stroma were stained.

Adenosine triphosphatase. The acinar cells

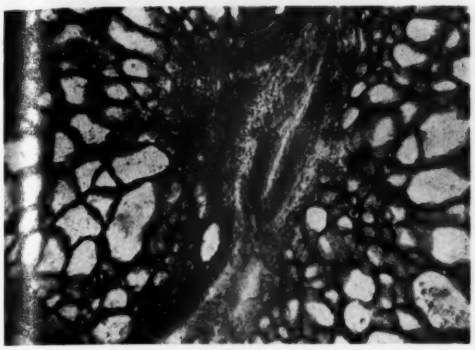

FIG. 1.

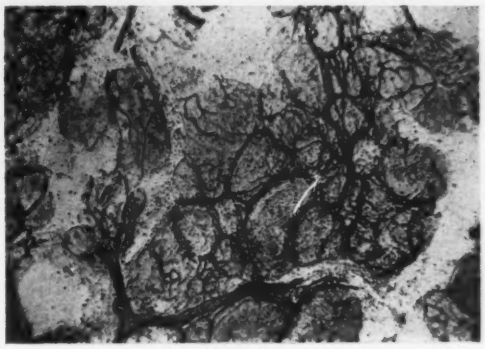

FIG. 3.

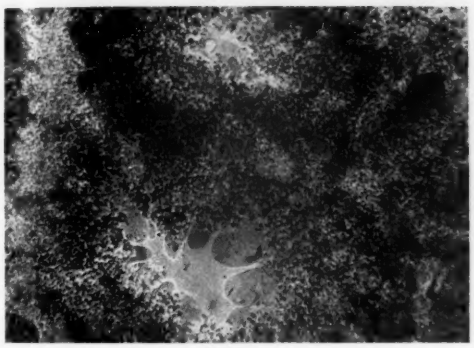

FIG. 2.

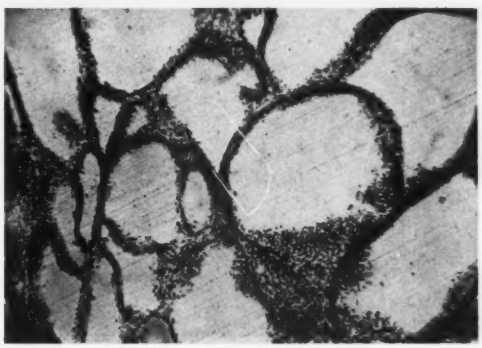

FIG. 4.

FIG. 1. Diphosphopyridine nucleotide diaphorase. Adenomatous colloid goiter. Acinar cells show moderate activity. Interstitial tissue and vascular wall are also reactive. ×15.

FIG. 2. Succinic dehydrogenase. Adenomatous colloid goiter. Mitochondria appear as uniform, fine, deeply stained granules or rodlets. ×436.

FIG. 3. Adenosine triphosphatase. Adenomatous colloid goiter. Acinar cells are unreactive. Connective stroma with apparent increased fibrosis is seen. ×44.

FIG. 4. Acid phosphatase. Adenomatous colloid goiter. Nuclear activity is marked. ×44.

showed no reaction in normal and abnormal thyroid glands studied. The stroma and vascular walls showed marked activity and stained dark brown.

Alkaline phosphatase. In normal and adenomatous colloid goiters, no activity was noted in the acinar cells. However, moderate focal intracytoplasmic activity was observed at the follicular border of acinar cells. The stroma was faintly reactive. Colloid substance stained occasionally and appeared brownish in color.

Acid phosphatase. Nuclear element of the acinar cells showed moderate activity. Colloid substance did not stain. In hyperplastic glands rather dense intracytoplasmic deposits of stain were found at the follicular border of the cells. In microfollicular adenomas, moderate hyperactivity was noted.

Esterase, nonspecific. Nonspecific esterase activity was characterized by the presence of small dark blue intracytoplasmic granules. The colloid substance was occasionally stained and appeared pink-yellow in color. In areas of glandular hyperplasia there seemed to be a slight accumulation of such granules. The stroma and vascular patterns were unreactive.

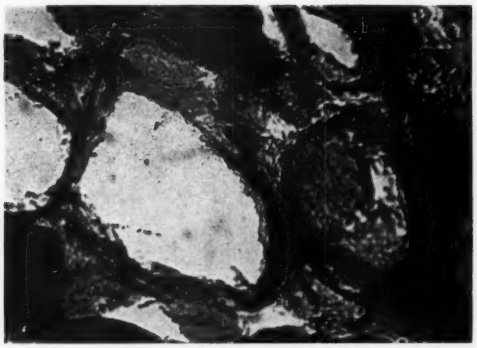

FIG. 5.

FIG. 7.

FIG. 6.

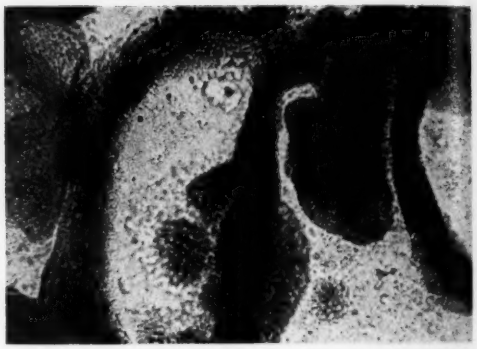

FIG. 8.

FIG. 5. Alkaline phosphatase. Adenomatous colloid goiter. Epithelial cells are unreactive. Stroma shows moderate activity. ×44.

FIG. 6. Nonspecific esterase. Adenomatous colloid goiter. Marked intracytoplasmic activity is characterized by appearance of coarse bluish granules. ×44.

FIG. 7. Succinic dehydrogenase. Microfollicular adenoma. Definite increase of activity in adenomatous area is seen as compared with the normal appearing gland. ×44.

FIG. 8. Diphosphopyridine nucleotide diaphorase. Diffuse hyperplasia of thyroid treated preoperatively with diac. Even though the follicular cells appear hyperplastic and hyperactive, the enzyme activity seems to be significantly diminished. ×44.

Table II contains a summary of histochemical enzyme pattern observed in the various types of thyroid gland studied.

DISCUSSION

In general, no significant enzyme change was noted between normal thyroids and adenomatous colloid goiters. It appeared that the enzymes, diphosphopyridine nucleotide diaphorase and succinic dehydrogenase, were evenly distributed in acinar epithelial cells. The mitochondria were consistently demonstrable as round or rodlet structures. They seemed to be mostly localized peripherally beneath the cytoplasmic membrane. In none of the cases were mitochondrial degenerative changes seen. The degree of activity of these enzymes seemed to be directly related to the height of the epithelial cells. Tall, columnar cells appeared to stain more deeply than the cuboidal and flat cells. This phenomenon was particularly outstanding in diffuse hyperplastic thyroids treated with itrumil sodium or iodine. Occasional small foci of hyperactive, hyperplastic, and hyperchro-

TABLE I.—DISTRIBUTION OF ENZYMES IN THE NORMAL THYROID GLANDS

	Colloid	*Follicular cells*	*Basement membrane*	*Capillary walls*	*Stroma*
1. Succinic dehydrogenase	−	++	−	−	−
2. Diphosphopyridine nucleotide diaphorase	−	++	±	+	+
3. Glucose-6-phosphatase	−	−	+	−	−
4. Adenosine triphosphatase	−	−	++	++	+
5. Acid phosphatase	−	+	−	−	−
6. Alkaline phosphatase	±	−	+	±	±
7. Nonspecific esterase	±	++	−	−	−
8. Oxidase		++			
9. Peroxidase	−	+			
10. Beta-d-glucuronidase	−	++			
11. Glycerophosphatase, alkaline	−	+			
12. Glycerophosphatase, acid	−	±			
13. Proteolytic enzyme	+				

TABLE II.—ACINAR ENZYMATIC PATTERN IN VARIOUS DISEASES OF THE THYROID GLAND

	*ACG**	*Diffuse hyperplasia*	*Microfollicular adenoma*
No. of specimens	23	7	2
Succinic dehydrogenase	++	++ to +++	+++
Adenosine triphosphatase	−	−	−
Diphosphopyridine nucleotide diaphorase	++	++ to +++	+++
Glucose-6-phosphatase	−	−	−
Alkaline phosphatase	−	±	−
Acid phosphatase	±	+	++
Nonspecific esterase	++	+++	+++

*ACG, Adenomatous colloid goiter.

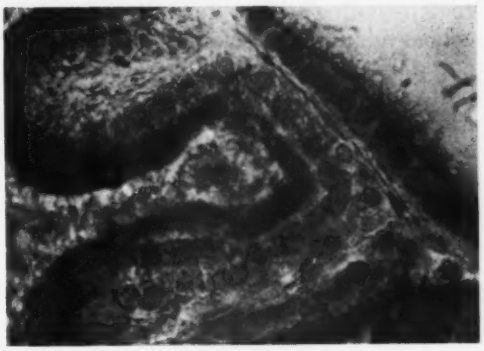

FIG. 9.

FIG. 10.

FIG. 9. Acid phosphatase. Diffuse hyperplasia of thyroid. Moderate intracytoplasmic activity is seen at the acinar border of hyperactive cells. Nuclei are faintly reactive. ×196.

FIG. 10. Alkaline phosphatase. Diffuse hyperplasia of thyroid. There appears to be present moderate intracytoplasmic activity in the hyperactive follicular cells. ×196.

matic cells were encountered in such specimens. In contrast, in a case of thyroid preoperatively treated with diac, it appeared that the enzyme activity was significantly diminished even though the epithelial cells remained tall and hyperplastic.

Previously, enzymatic histochemistry of the thyroid gland has been the subject of limited investigations. The enzymes studied included: oxidase, peroxidase, 5-nucleotidase, phosphatases, and beta-d-glucuronidase. The results of these studies are included in Table I.

Significant suppression in oxidative—peroxidase and cytochrome oxidase—activity of the thyroid gland subsequent to therapy with antithyroid drugs has also been observed by Dempsey (1), DeRobertis and Franklin.

Appearance of moderate alkaline and acid phosphatase activity in cytoplasm of the more active acinar cells, as observed in our experience, has also been noted by Dempsey (2).

SUMMARY

Enzymatic histochemical techniques were applied to 35 fresh surgically resected thy-

roids including normal glands, adenomatous colloid goiters, microfollicular adenomas, and diffuse hyperplasia. The enzyme distribution in the normal and diseased gland is described. Also, the effect of antithyroid drugs on oxidative activity of the gland is noted.

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AN EXPERIMENTAL STUDY OF FIBRINOLYSIS IN THE PROPHYLAXIS OF PERITONEAL ADHESIONS

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THE SURGICAL ENIGMA of peritoneal adhesions presents a challenging problem from the standpoint of both cause and prophylaxis. It is apparent from a review of the literature that to the present time only two means of prophylaxis have been firmly established: minimum peritoneal damage at the time of operation and the prevention of intraperitoneal infection. It is obvious that these two factors cannot be eliminated entirely in practice, and therefore the need for a supplementary mode of prophylaxis remains an urgent problem justifying periodic consideration.

In the past, work has been carried out on methods of prevention of adhesions by using: increased intestinal motility, intraperitoneal instillation of air, grafting, oversewing, clot prevention using heparin and other anticoagulants, instillation of hypotonic solutions, prevention of infection, hyaluronidase, steroids, and fibrinolysis. In no instance, has the effectiveness of any method been conclusive.

In 1954, Cliffton and his associates (2, 3) demonstrated that clot lysis in vivo could be produced by fibrinolysin, a proteolytic enzyme. Since then the great potential of this material has been explored by many investigators as a means of rapidly dissolving intravascular clots. Fibrinolysin is prepared by extracting plasminogen from fraction III-3 of plasma and usually activating it with streptokinase. Fibrinolysin is a substance native to the body with a physiologic activity rendering it suitable for lytic function within the peritoneal cavity if appropriate concentration can be produced there. The promise of this material led us to explore its use as a possible fibrinolytic agent in the prophylaxis of peritoneal adhesions.

From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia.
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METHODS AND MATERIALS

Two experimental series were carried out employing a total of 52 male albino rats of the Wistar strain ranging in weight from 190 to 210 grams. The animals were maintained under routine laboratory conditions. Light ether anesthesia was used and sterile operative technique was practiced in all procedures.

Experiment I. Our first experiment was carried out to determine if the incidence of peritoneal adhesions resulting from mechanical trauma to the bowel was influenced by the use of fibrinolysin. Thirty-six animals were used. Each animal underwent trauma to the bowel by crushing of the cecum using a Kelly hemostat which was closed completely for a fixed length of time. This method was described and standardized by Thomas and associates and was shown to produce adhesions in 100 per cent of cases. After trauma to the cecum, the animals in the experimental groups received varying doses of fibrinolysin[1] intraperitoneally.

CONTROL GROUP. Six animals were used. Each underwent the following procedure: The peritoneal cavity was opened through a lower abdominal midline incision 3 centimeters in length. A small self-retaining retractor was inserted and opened. The cecum was identified and withdrawn through the incision with toothless forceps and placed on a sterile gauze sponge

[1]The fibrinolysin used in this study was lyophilized actase® fibrinolysin (human).

FIG. 1. An example of a control animal demonstrating dense adhesions from the traumatized area of the cecum to adjacent bowel and mesentery.

moistened with physiologic saline solution. A Kelly hemostat, which was labelled and used in all the procedures in this experiment, was applied full length to the cecum and completely closed for exactly 30 seconds, then removed. The traumatized cecum was then returned to the peritoneal cavity, and the peritoneum and overlying muscle were closed with a double row of continuous suture of No. 4-0 black silk. The skin incision was closed with interrupted sutures of No. 4-0 black silk. The operating time was about 10 minutes.

In 3 of the 6 control animals, 3 milliliters of sterile physiologic saline solution were instilled intraperitoneally as a control for the fluid volume factor in the experimental groups.

EXPERIMENTAL GROUPS. Thirty animals were used in this experiment as follows:

Group A. Six animals underwent the same procedure as the control group; however, after the muscle layer was sutured, 13,000 units of fibrinolysin were instilled intraperitoneally and then the skin was closed. The fibrinolysin solution was prepared immediately after the muscle layer was closed by injecting 3 milliliters of sterile physiologic saline solution into a sealed vial containing 13,000 units of lyophilized fibrinolysin. This material was injected intraperitoneally through the exposed muscle layer to the right of the operative incision and the skin was closed. This method was adopted to avoid loss of fibrinolysin while the incision was being sutured.

Group B. Eight animals underwent the same procedure as the control group, and then were given intraperitoneal injections of 19,500 units of fibrinolysin in 3 milliliters of physiologic saline solution immediately postoperatively.

Group C. Fourteen animals underwent the same procedure as the control group, and then were given intraperitoneal injections of 26,000 units of fibrinolysin in 3 milliliters of physiologic saline solution immediately postoperatively.

Group D. Two animals underwent the same procedure as the control group, and then were instilled with a total of 26,000 units of fibrinolysin given in 2 doses through an indwelling plastic catheter. The first 13,000 unit dose was given immediately postoperatively and the second doses 24 hours later.

Experiment II. An additional experimental study was undertaken to determine the effect of varying doses of fibrinolysin on wound healing of the abdominal and colonic walls. Sixteen animals were used. Each animal underwent transection and immediate resuture of the ascending colon under aseptic conditions employing No. 4-0 black silk in a single layer. The operating time was about 30 minutes.

CONTROL GROUP. Five animals were used as the control group.

EXPERIMENTAL GROUPS. Eleven animals were used in this experiment as follows:

Group A. Five animals were injected intraperitoneally with 13,000 units of fibrinolysin immediately postoperatively.

Group B. Four animals were injected intraperitoneally with 26,000 units of fibrinolysin immediately postoperatively.

Group C. Two animals received 26,000 units of fibrinolysin intraperitoneally given in 2 doses through an indwelling plastic catheter at an interval of 24 hours.

RESULTS

In all 52 animals, reoperation was carried out 7 days after the initial procedure—adhesion formation is completed within 3 to 6 days after injury—using a right rectus incision so that healing of the initial incision as well as the peritoneal contents could be observed. Three classifications were used in grading the extent of adhesion formation in the animals reoperated upon: (1) dense adhesions—adhesions occurring from the traumatized area of the cecum to the adjacent bowel, mesentery, and abdominal wall; (2) minimal adhesions—1 or 2 strands

of fibrinous tissue occurring from the traumatized area of the cecum to the adjacent mesentery; (3) no adhesions—entire peritoneal cavity and abdominal wall free of adhesions.

Experiment I. Dense adhesions occurred in all 6 control animals. In group A of the experimental animals, 13,000 units fibrinolysin, minimal adhesions occurred in 5 of 6 animals, while no adhesions were present in the animal remaining. All 8 animals in group B, 19,500 units fibrinolysin, were free of adhesions and all but 2 of the 14 animals in group C, 26,000 units fibrinolysin, were also adhesion-free. In group D, 26,000 units in 2 doses, minimal adhesions occurred in 1 animal, while no adhesions could be found in the other animal in this group. Thus, in 36 animals, dense adhesions occurred in 6, minimal adhesions in 8, and no adhesions in 22. Chi square analysis revealed statistical significance in comparing controls and experimental group C.

Experiment II. To evaluate the results of the second series of experiments, random sections of the abdominal wall through the site of wound closure and sections through the colonic anastomosis were taken from control and experimental animal groups, fixed in formalin, and prepared for histologic study. Microscopic study of these sections revealed that wound healing in the experimental groups was normal in all respects as compared to control sections. There was no instance of perforation or gross abnormality of the colonic suture line, and nothing to suggest the presence of peritonitis.

DISCUSSION

Peritoneal adhesions form as a dynamic nonspecific response to injury. The natural history of peritoneal adhesion formation appears to include: trauma followed by capillary dilatation, stasis, increased capillary permeability, transudation into the peritoneal cavity and the resultant formation of a fibrinous clot accompanied by a diminution in peristaltic activity. Opie, in microscopic observations on inflammatory

FIG. 2. An example of experimental animal, experiment I, group B, demonstrating the absence of peritoneal adhesions following the use of 26,000 units of fibrinolysin.

exudate, noticed an increase in polymorphonuclear leukocytes in the exudate within 6 to 24 hours after trauma. He further described a disintegration of the leukocytes in 72 to 96 hours with the release of proteolytic enzymes. These enzymes, he thought, were responsible for the breakdown of the fibrinous network and its subsequent absorption into the lymphatics. The probable role of fibrinolysin in this process is the aiding of natural body mechanisms in destruction of the fibrinous exudate resulting in the prevention of permanent dense adhesions. All previous experimental attempts at prevention of adhesion formation were based on interruption of the natural history, as already defined, at some stage other than that affected by fibrinolysin.

From previous studies of Cliffton (1) and Moser in animals and man, it is known that fibrinolysin possesses some toxic properties when administered intravascularly. No previous studies are recorded concerning its toxic character when administered intraperitoneally. From our knowledge of the exuberant vascular supply to the peritoneum and its vast absorptive surface, it is reasonable that the same toxic manifestations, perhaps somewhat delayed, would be present after intraperitoneal administration of this material. The major toxicity has been a

febrile response of a mild to a moderate nature and occasional depression of fibrinogen and prothrombin level. In our study, fibrinolysin was administered to a total of 51 animals. Eleven received 13,000 units, 8 received 19,500, and 4 received 26,000 units in divided doses; none of these animals exhibited toxicity. Of the 28 animals receiving 26,000 units in a single dose, 9 died within a period of 30 minutes. Postmortem examination of each of these animals revealed extensive hemorrhage into the pulmonary parenchyma without other evidence of hemorrhagic diathesis. Histologic study of the involved tissues revealed extensive hemorrhage into areas of infecton. The prophylactic use of chlortetracycline in later animals eliminated this hazard completely.

It is known that in man approximately 300,000 units of fibrinolysin can be administered with safety. Studies of the fibrinolytic systems of dogs and other lower animals suggest the presence of inhibitor substances. Accordingly, it is impossible to equate an optimal dosage in the rat on a weight for weight basis with man.

A reasonable clinical application of this work is the use of fibrinolysin immediately after abdominal surgery, except in those instances in which infection is present, i.e. peritonitis. A further extention might be the instillation of this material into the brain or dural areas after cranial surgery or trauma to lessen the possibility of seizures as a result of scar formation. The use of fibrinolysin would greatly facilitate the repair of damaged or severed tendons, resulting in a more rapid and more complete return to normal function.

SUMMARY

1. An experimental study of the effects of fibrinolysin on peritoneal adhesion formation was carried out.

2. Fibrinolysin was shown to have a statistically significant action in the prevention and reduction of peritoneal adhesions.

3. Additionally, this material had no adverse effects on abdominal wall or colonic wound healing.

4. The toxic properties of the experimental agent are discussed.

5. Practical clinical application is cited.

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SACROCOCCYGEAL CHORDOMAS

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IN A PREVIOUS ARTICLE a new technique was described (4) for the resection of sacral and presacral tumors in which the co-operative efforts of a neurosurgeon, general surgeon, and orthopedic surgeon were employed. Follow-up data concerning 18 patients who had sacrococcygeal chordomas treated by this method are now presented. These patients include 6 previously reported upon in the original paper and 12 who have been operated upon since that time.

In this series, there are 15 men and 3 women. The higher incidence of chordoma in males has been reported previously by Dahlin, Littman, Gentil, Swinton and their associates. The ages of the patients at operation ranged from 38 to 69 years, the average age being 55 years. The longest interval between operation and follow-up study was 12 years and the shortest, 1 year. Six deaths occurred during the follow-up period, 1 in the hospital. Five patients have survived, although with evidence of recurrence, and 7 are living without evidence of recurrence to date.

DEATHS

The hospital death was of a 61 year old man in whom a massive pulmonary embolus developed 10 days after operation. A second patient died of coronary thrombosis 19 months after operation. The other 4 deaths resulting from the tumor occurred 4, 4½, 6, and 7 years after the original operation. In 2 of these patients there had been clinical evidence of distant metastatic processes to the bones and lungs. Necropsy, unfortunately, was not performed in these last 2 cases.

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PATIENTS ALIVE WITH RECURRENCES

Five patients are alive but have had a recurrence of the tumor. The length of survival of these 5 patients since the original operation at the Mayo Clinic is 5, 6, 7, 8, and 9 years, respectively. All 5 of these patients have returned one or more times for reoperation for the excision of recurrent tumor nodules. One patient has undergone excision of recurrent nodules 5 times since the original operation was performed 7 years previously. One patient had been operated upon elsewhere prior to surgical treatment. Some spillage of tumor tissue into the wound occurred during resection in the other 4 patients. At the time of this study, 1 of these patients presumably had generalized metastatic involvement 9 years after the original operation.

PATIENTS ALIVE WITHOUT RECURRENCE

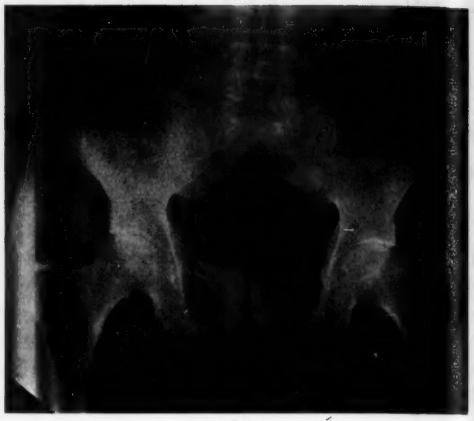
At the time of this report, 7 patients were alive without recurrence after excision of chordomas by the co-operative technique. The length of survival was 1, 2, 3, 4, 8, 9, and 12 years, respectively. Two of these patients underwent the original operations elsewhere, but the definitive surgery, with partial sacral resection, was performed by us.

Thus, we have 3 long term survivals of 8, 9, and 12 years without evidence of recurrence of tumor after total resection of sacrococcygeal chordoma (Table I).

POSTOPERATIVE COMPLICATIONS

Retention of urine was the commonest postoperative complication. It developed in

a



b

FIG. 1. a, Preoperative roentgenogram, 12 October 1950, showing a chordoma of the lower segments of the sacrum. b, Roentgenogram, 14 September 1960, almost 10 years after resection of the sacrum. There is no evidence of recurrence.

9 patients, 50 per cent, 8 men and 1 woman. Three transurethral prostatic resections were performed upon patients still in the hospital because of inability to void satisfactorily. There was associated prostatic hyperplasia. The amounts of prostatic tissue removed were 70, 24, and 10 grams. After resection, all 3 patients voided normally. The volume of residual urine of 3 patients varied from 10 to 35 cubic centimeters at dismissal. In 2 patients, the volume of residual urine was 200 and 650 cubic centimeters at dismissal. However, since the function of the bladder was improving in both, they were dismissed, and when seen some time later both were voiding normally. At dismissal, a volume of 1,000 cubic centimeters of residual urine was recorded in the 1 woman with retention and instructions were given for daily catheterization. Some months later, voiding was normal, and cystoscopy showed the bladder to be normal except for a marked cystocele. None of these patients had bilateral loss of sensation in the perineum. In only 1 patient was there unilateral sensory loss in the perineum and scrotum.

Infection developed in the wounds of 3 patients, which is not surprising in view of the proximity of the operative site to the anus; and in 1 patient disruption of the wound occurred, which necessitated secondary suture.

A fistula draining cerebrospinal fluid, which required repair, developed in 1 patient. A fecal fistula, for which proximal colostomy was performed, occurred in another.

One patient was found, upon return, to have a large sacral hernia which was producing a distressing, dragging sensation in the abdomen. Repair of the hernia relieved this distress.

ROENTGENOTHERAPY

Thirteen of the 18 patients received roentgenotherapy. Of the 6 patients who died, 5 received irradiation. Of the 5 who were alive with recurrences at the time of writing, all had received irradiation after operation. Of the 7 patients without recurrence, 1 patient had received irradiation preoperatively, 3 had received irradiation postoperatively, and 3 had not been so

treated. Two of the long term survivors received irradiation and 1 did not.

SURGICAL TECHNIQUE

The patient is placed in the prone position with the buttocks elevated and the trunk and thighs flexed. A midline incision is made over the sacrum down to the anal ring. The coccyx is freed and is retracted posteriorly or excised, and the rectum is freed up from the coccyx and sacrum. The tumor is identified, and, with osteotome and scissors dissection, the ligaments, muscles, and a portion of the sacrum are incised wide of the tumor. The nerves—and especially the pudendal—are protected when possible. The tumor, with the adjacent portion of sacrum and ligaments, is then removed and the resulting defect is closed by approximation of the muscles and fascia.

The coccyx and the lower 3 sacral segments of the vertebrae may be removed. More extensive removal may cause collapse of pelvic bones and descensus of the lumbar vertebrae (Fig. 1a and b). The upper 3 sacral nerves should be preserved unilaterally and preferably bilaterally. Preservation usually can be accomplished if the lower 3 sacral segments are removed.

COMMENT

The treatment of sacrococcygeal chordomas has been unsatisfactory in the past because of the almost invariable local recurrence of the lesion with ultimate metastasis. The only "cure" known to us is that which Dahlin and MacCarty reported in 1952, which concerned a man who died at the age of 83 years of a cerebral infarct, 23 years after treatment of a sacrococcygeal chordoma by a combination of surgical measures, roentgen-rays, and radium. In a comprehensive review of the literature in January 1953, Littman collected 165 cases previously reported and added 3 of his cases, making 168 in all. He wrote that a thorough search for a report of a "cure" had been fruitless. Gentil and Coley, writing in 1948, were of the same opinion, observing that local recurrence after surgical excision is a constant feature. Thus, the problem is that of a tumor which tends to recur locally and which is associated with a very ominous prognosis. The incidence of distant metastases, to judge by the figures of Littman, Gentil and Coley, and Swinton and Lehman, is 10 per cent. Three patients in our series, or 16.6 per cent, are presumed to have distant metastases.

TABLE I.—SURVIVAL AMONG 18 PATIENTS OPERATED UPON WITH AND WITHOUT RECURRENCES

Yrs. after operation	*Living with*		*Total living*
	Recurrence	*No recurrence*	
1		1	1
2		1	1
3		1	1
4		1	1
5	1		1
6	1		1
7	1		1
8	1	1	2
9	1	1	2
10			
11			
12		1	1
Total	5	7	12

We believe that adequate block resection of the sacrum by means of the combined technique offers the best prospect of eradication of these tumors and that such a procedure favors a low operative mortality rate and a reasonably low morbidity rate. We also believe that as palliative measures, repeated resections of recurring tumor, when feasible, increase the survival time and add to the patient's comfort. However,wide resection when the patient is first seen offers the best prospect of cure, if indeed cure can be anticipated. Spillage of tumor cells should be avoided if at all possible, for implantation is a common feature of these tumors, as it is of chondrosarcomas. However, avoidance of this type of spillage sometimes is not possible because of the friability of the tumors.

Although 50 per cent of our patients had transient retention of urine, none had permanent incontinence or excessive retention of urine. We believe that retention of urine can be avoided if the upper three sacral nerves can be preserved at least unilaterally.

Retention of urine occurs if the third, fourth. and fifth sacral nerves, or both pudendal nerves, are cut bilaterally. These observations are substantiated by a review of our entire series of sacral and presacral tumors of all types.

CONCLUSIONS

1. We have presented a follow-up study of 18 patients operated upon at the Mayo Clinic for sacrococcygeal chordomas by a technique which employed the co-operative efforts of a neurosurgeon, general surgeon, and orthopedic surgeon.

2. Six patients died during the follow-up period—1 during hospitalization. Two died from causes unrelated to the lesions and 4 died of the tumors—2 with presumed generalized metastasis.

3. Five patients were alive but with recurrence at the time of this report, and 1 of these is presumed to have generalized metastasis.

4. Seven patients were alive without evidence of recurrence as this report was written, and 3 of these had survived 8, 9, and 12 years after operation.

5. We believe that the procedure we have described offers some prospect of cure, if cure of such lesions can be anticipated, and in most instances the procedure will permit retention of normal function of the bladder and bowel.

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THE EFFECT OF TISSUE TEMPERATURE ON THE BINDING OF ALKYLATING AGENTS IN THE ISOLATION PERFUSION TREATMENT OF CANCER

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THE CLINICAL USE of the isolation perfusion technique for cancer chemotherapy has been limited by the severe toxicity that can result from systemic admixture of the drug employed. Isolation in a limb by application of a tourniquet is relatively easy to achieve but must be accomplished in other parts of the body by other techniques. This study has demonstrated that "relative" isolation by a short period of exposure to a high dosage of drug can be effective if tissue temperature is maintained at a high level. Markedly greater amounts of drug will bind in a short period of time to hyperthermic tissue and then in a longer period of time to hypothermic tissue.

BACKGROUND

The technique of isolation perfusion was developed as an outgrowth of work of such investigators as Grady and Klopp (6, 7) who injected tumoricidal chemotherapeutic agents by the intra-arterial route in order to effect a greater binding of these drugs to localized tumors and avoid the toxic systemic effects of the agents on the remainder of the body. The direct intra-arterial injection of nitrogen mustard presented difficulties. In many instances, this agent produced local arterial thrombosis because of its vesicant action. In addition, it did not remain in the tumor circulation long enough to bind a sufficient amount of the drug to the neoplastic tissue, and thus the full effectiveness of the agent was not realized. The drug mixed rapidly with the general circulation and caused toxicity to the lymphatic and hematopoietic systems. The work of Creech and his associates (1, 2, 9) and Stehlin in isolation perfusion provided the first effective means of high dosage administration of chemotherapeutic agents without profound systemic toxicity.

The isolation perfusion technique which effects the "relative" isolation of a tumor-bearing area depends not only upon a short period of tissue exposure to a high dosage of drug but also upon the fact that the neoplastic tissue in the perfused area is more susceptible to the chemotherapeutic agent than is the normal tissue. This technique involves the maintenance of the circulation of the perfused area by the use of an extracorporeal pump oxygenator, which preserves tissue metabolism in the involved area.

The use of an oxygenator was thought to be of value in this technique since, if normal oxygenation were maintained, normal metabolism could be expected to continue. Also, the experimental evidence of Gray (4) and other investigators has shown that high tissue oxygen tension potentiated the effects of ionizing irradiation upon tumor tissue. It was postulated that it would also potentiate alkylating agents, the type of chemotherapeutic agent most widely utilized in the isolation perfusion technique, because they are radiomimetic in many of their actions.

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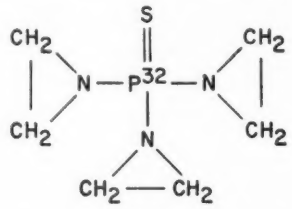

FIG. 1. Chemical structure of P^{32}-tagged triethylenethiophosphoramide.

Problems in clinical use of isolation perfusion. Clinical reports on the application of the isolation perfusion technique have revealed several inherent problems. There are local effects upon normal tissue, such as edema, erythema, vesiculation, and, in some instances, peripheral neuritis, but they are relatively unimportant. The main causes for concern are the systemic effects which result from the high dosage of chemotherapeutic agent that circulates throughout the body because of the mixture of the perfused and systemic circulations. Many methods to decrease this admixture of drug by improving isolation have been evolved. The use of pneumatic tourniquets during perfusion of the extremities has helped, as has a more effective dissection of collateral circulatory channels. By a more effective venous dissection, a zone of comparatively higher venous pressure surrounding the perfused area is created. The low venous pressure produced by suction at the venous cannula not only theoretically but also clinically reduces the amount of spillover into the systemic circulation. Also low arterial flow rate in the perfused circulation, causing the arterial pressure in the perfused area to be less than the systemic pressure, allows the remaining collateral arterial circulation to flow into, rather than out of, the perfused area. The use of agents such as papaverine in the perfusate, which by vasodilatation effectively decrease arterial and arteriolar resistance, again effectively lowers arterial pressure.

In spite of these various measures, systemic admixture with resultant toxicity has continued to be a problem in isolation perfusions other than those performed on the extremities. This difficulty has led Shingleton and Parker to utilize systemic hypothermia to decrease further the collateral circulation around the perfused site.

Temperature as a variable in the improvement of the binding process. We thought that a fruitful investigation could be performed on the effect of temperature upon binding of the chemotherapeutic agent in vivo, that is, to evaluate whether or not hyperthermia would increase metabolism and binding of drug to the local tissues. Our convictions about the value of such a study stemmed from observations that during the course of an isolation perfusion, the arterial and venous oxygen saturations appeared to approach similar values with less and less utilization of oxygen. This fact indicated that during the course of an isolation perfusion, some other variable tended to diminish the metabolism of the perfused area. Temperature was selected as a possible variable since it was also noted that the temperature of the tissue in the isolated area would drop to a level 6.7 to 9.4 degrees C. lower than its normal temperature, because a large volume of blood in the oxygenator circuit was exposed to room temperatures during the procedure. Theoretically, the reduced metabolism could result in a decreased binding of the alkylating agent in the local tissues and also in more systemic spill, since a greater concentration of drug would be circulating for a longer period of time rather than being bound to the tissues in the isolated circuit.

METHODS

Experimental procedure. The agent selected for use in this experimental series, because an atom of phosphorus is included in the molecule, was triethylenethiophosphoramide, an alkylating chemotherapeutic agent of the ethylenimine series. Radioactive phosphorus (P^{32}) is a relatively high energy beta particle emitter, and its use facilitates measurement of the quantities of drug bound during the course of a perfusion. P^{32}-tagged triethylene-

thiophosphoramide (thioTEPA) (Fig. 1) would theoretically be metabolized in the same manner as the nonradioactive compound. At the cellular level, the sulfur would be broken off the molecule first; then a further split would free the phosphorus and leave 3 ethylenimine groups available for alkylation.

Mongrel dogs were anesthetized intravenously with pentobarbital and an incision made over the superficial and common femoral arteries at the groin. After adequate dissection, during which collateral arterial and venous channels were occluded, the femoral vein was cannulated (Fig. 2), and blood was passed through a Sigmamotor pump into the venous side of a disposable "bubble-type" oxygenator. Blood then flowed from the arterial reservoir and passed again through a Sigmamotor pump; from there it flowed through a water-jacket type of heat exchanger and then back into the femoral artery through a second cannula. All animals were given heparin as an anticoagulant in a dosage of 2 milligrams per kilogram of body weight.

After an adequate flow had been established, a rubber tourniquet was passed around the upper thigh of the animal, and the isolation perfusion was begun. Perfusions were maintained for a period of 1 hour after the temperature of the tissue had stabilized at the level determined for the particular experiment. When the temperature of the tissue had arrived at this designated level, thioTEPA, approximately 1 milligram per kilogram of body weight, was injected into the arterial side of the pump oxygenator circuit. Temperature monitoring of the circulating arterial blood and of the water bath which surrounded the blood in the heat exchanger was maintained. The temperature of the tissue was monitored with a thermistor probe placed in a standard location in each experiment at a level just above the knee joint of the experimental animal.

After completion of the perfusion, the perfused blood was drained from the circuit

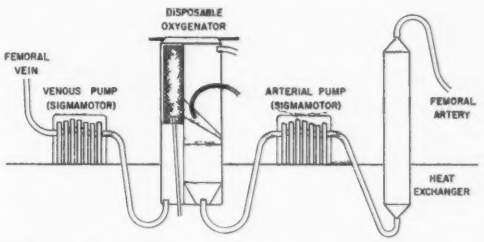

FIG. 2. Perfusion circuit used in experimental work.

and the limb was washed with 2 units of blood containing no chemotherapeutic agent. The vessels were then repaired, and the anticoagulant effects of the heparin were counteracted by the use of polybrene®.

Evaluation procedure. The level of the admixture of the perfusate with the systemic circulation was measured by administering radioactive chromium (Cr^{51})-tagged erythrocytes and then sampling systemic blood throughout the course of the perfusion. From these blood samples measurement of the concentration of Cr^{51}-tagged erythrocytes entering the systemic circuit was made. A more accurate measure of the total quantity of perfusate that entered into the systemic circulation was derived from a blood volume determination using Cr^{51}-tagged erythrocytes. The erythrocytes were tagged with radioactive sodium chromate using Talbot's modification of the original Gray and Sterling technique (5). Blood volumes were calculated by using the methods described by Rochlin and associates (8). The amount of mixing of the perfusate with the systemic circulation was found to be no greater than 4 per cent in any experiment; accordingly, these values were discarded from the later calculations.

At the end of each experiment the quantity of drug returned in the wash was determined by measuring the total volume of the wash and counting several aliquots of this total volume on planchets using the beta-sensitive anthracene crystal scintillation detector. The proportion of tagged chemotherapeutic agent in the wash was determined from the total radioactivity injected minus

TABLE I.—TABULATION OF DATA OBTAINED IN THE EXPERIMENTAL ANIMALS

Dog No.	*Weight, kgm.*	*Tissue temperature, centigrade*	*Drug returned, per cent*	*Counts/min./ 100 mgm. tissue, corrected*
1	12.8	23.9	74	145
2	16.4	24.4	81	108
3	22.0	24.4	68	117
4	13.8	26.1	73	128
5	15.0	26.7	86	133
6	22.0	31.1	52	162
7	14.0	32.8	85	130
8	12.0	33.3	46	27
9	17.7	33.3	60	56
10	10.4	35.0	43	46
11	12.6	35.0	36	38
12	18.0	35.0	33	71
13	10.8	35.0	38	42
14	23.4	36.7	37	15
15	17.4	36.7	11	8
16	16.0	37.2	17	17
17	17.3	37.8	25	6
18	19.9	37.8	18	5
19	23.0	38.9	9	9

The counts per minute per 100 milligrams of tissue have been corrected for the weight of a standard animal and a standard quantity of administered isotope.

a correction factor for the amount of radioactivity remaining in the syringe after injection. Thus, from the amount of drug returned and from the total amount administered, the percentage of drug not bound during the course of the perfusion was calculated. A representative portion of muscle tissue was removed from a standard location in the leg of each animal at the completion of the experiment. Several sections were then cut with a hand microtome, washed several times with isotonic saline, and then counted on planchets using a beta-sensitive anthracene crystal. The samples were then desiccated, and the weight of the dry sample was determined. The peripheral blood samples were counted for Cr^{51} activity using a sodium-iodine crystal in a well-type scintillation detector.

Evaluation of tissue samples was considerably more difficult than determination of the unbound drug in the wash. As previously mentioned, at the cellular level the alkylating portion of the triethylenethiophosphoramide molecule is separated off, and this molecular segment is actually bound to the tissue. The isotonic saline wash would remove remaining perfusate and free P^{32} in the extracellular space thus apparently causing a decrease in tissue radioactivity whereas binding of the drug to the tissues of the perfused area actually increased. Variations in the size of the hind limbs as well as variations in the quantity of isotope administered during each experiment made it difficult to standardize the quantity of drug bound between one animal and another. Accordingly, a set of correction factors was developed which not only allowed qualitative rather than quantitative comparison of the tissue samples but also attempted some standardization. The first correction factor was in terms of the number of counts per minute of P^{32} found per 100 milligrams of normal muscle tissue in each hind limb. The second correction took into account the change in the quantity of isotope administered because of the varying size of the animals. In this correction, an arbitrary standard of a 20 kilogram dog was used to correct the activity found in the samples by comparing the relative weight of the experimental animals to that of a standard 20 kilogram dog. The third correction factor resulted from calculation of the number of 10^6 counts per minute of isotope administered to each animal. The actual numerical values for tissue activities are thus standardized in terms of counts per minute per 100 milligrams of tissue per 20 kilogram dog per million counts given. We recognize that this numerical value is an artificial attempt at comparison of one tissue sample with the next, but believed that an effort to standardize the activity in the various samples was necessary.

RESULTS

Nineteen experimental animals were operated upon and underwent isolation perfusion of the hind limb. Table I is a tabulation of the results of these studies. As can be seen from the calculated values of the percentage of drug returned, statistical correlation between the tissue temperatures of one animal and another is not possible. However, an analysis of the entire series demonstrates that at any temperature below 26.7 degrees C. the minimal amount of drug re-

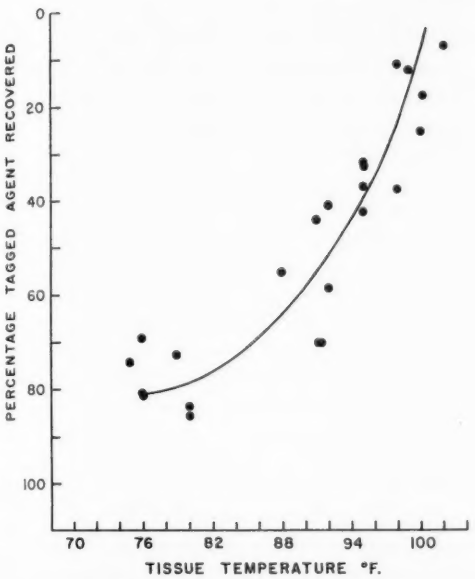

FIG. 3. The relationship of change in tissue temperature to binding of P^{32}-tagged triethylenethiophosphoramide perfused in the hind limb of mongrel dogs. The percentage of tagged agent recovered is based on the corrected value of agent administered.

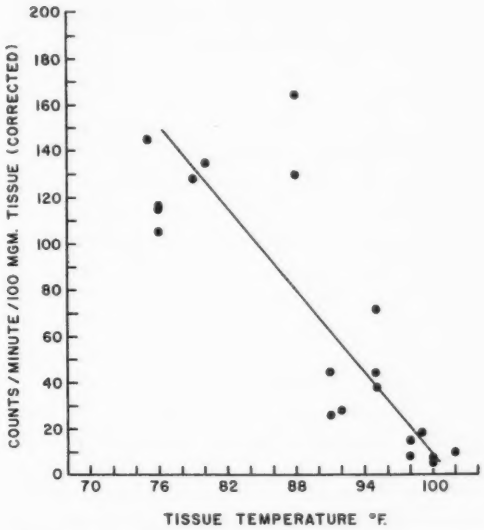

FIG. 4. The relationship of change in tissue temperature to the amount of tagged agent found in representative portions of tissue removed from the perfused area. The counts per 100 milligrams of tissue have been corrected for the weight of a standard quantity of isotope given.

turned in the wash was 68 per cent of the quantity administered. Less than one-third of the administered drug was bound to the local tissues during the course of a ½ hour isolation perfusion at these temperature ranges. These figures correlate well with the index of tissue activity administered—counts per minute per 100 milligrams of tissue corrected—in that these values also remained high.

Examination of the values obtained from perfusion at temperature ranges of 33.2 to 38.9 degrees C. show that the maximum quantity of drug returned at this temperature range amount to only 25 per cent of the administered dose, and 1 experiment at 36.7 degrees C. showed evidence of only 11 per cent of the drug being returned. These figures also correlate well with tissue activity—counts per minute per 100 milligrams of tissue corrected—in that this value varied from 5 to 17, indicating that a considerably larger quantity of alkylating agent was directly bound to the tissue, since the free P^{32} was removed during the washing procedure. In the midrange of temperatures, the figures for the percentage of drug returned, as well as the relative tissue activity, also correlate well. At the temperature ranges of 37.9 to 38.9 degrees C., increased postoperative edema was noted in the perfused extremity of experimental animals. This disappeared spontaneously, however, and in no instance was there a slough or necrosis of the normal tissue in the extremity.

Figure 3 is a graphic representation of the percentage of drug returned, indicating the direct relationship of drug-binding to elevation of temperature. It would appear from these figures that a more rapid rise in the rate of binding occurs at the higher temperature ranges than at either the low or middle temperature ranges.

The relationship of the P^{32} found in the muscle samples to the temperature rise appears to be almost a straight line reciprocal

relationship. Figure 4 is a graphic representation of this reciprocal correlation for the corrected figures in counts per minute per 100 milligrams of tissue.

DISCUSSION

Since the rate of any chemical reaction is a function of temperature, it is logical to find evidence of a direct correlation between the temperature in the local tissues and the rate of binding of an alkylating chemotherapeutic agent. The binding of alkylating agents is a chemical reaction varied by enzymatic metabolic changes, and it is reasonable that additional chemotherapeutic agent could be bound at a higher temperature.

A tissue temperature of 36.7 to 38.9 degrees C. is a hyperthermic state for the hind limb of the dog, and since the maximum binding occurred at a hyperthermic rather than a normothermic level, it is then apparent that a state of hyperthermia in the local perfused circuit will produce a more rapid binding of the chemotherapeutic agent.

The use of hyperthermia could theoretically produce problems when applied clinically, in that an increased binding of the drug in the local area might produce increased toxicity to the exposed normal tissues. For this reason, we have diminished the clinical dose of chemotherapeutic agent by approximately 25 per cent to compensate for this effect.

An important fact to be derived from this study is that, if a greater quantity of tumoricidal drug is bound per unit of time, and the mixing rate of the drug with the systemic circulation is a direct variable with time, then, with hyperthermic perfusion, less admixture of the drug with the systemic circulation would occur and less systemic toxicity. This effect is being evaluated clinically at the present time. It is also suggested that total body hypothermia, with its concomitant reduction in collateral circulation, combined with local hyperthermia and its effect on decreased systemic admixture and increased local binding, could be the ideal combination of factors.

At the present time, the numerical values of phosphorus activity in the tissues calculated in these experiments are but approximations. A corroboration of these results would be desirable through the use of thioTEPA tagged with a radioactive carbon-14 atom in one of the ethylenimine groups. In this way, the theoretic explanation for the reciprocal relationship between tissue temperature and tissue activity could be further documented.

Further studies with other isotope-tagged alkylating agents are indicated to substantiate the belief that this phenomenon occurs not only with thioTEPA but with other alkylating agents as well.

SUMMARY

The effectiveness of isolation perfusion techniques in the administration of chemotherapeutic agents for malignant tumors is limited by the degree of isolation obtainable by present methods, and consequently, by admixture and systemic toxicity. In an effort to study variables in "relative" isolation an investigation of the effects of local tissue temperature upon the rate of binding of P^{32}-tagged thioTEPA administered by isolation perfusion was performed. Nineteen experimental isolation perfusions were performed, using the hind limb of mongrel dogs.

A direct correlation between temperature and the rate of binding of the chemotherapeutic agent to the perfused tissue was demonstrated. Higher local tissue temperature markedly increased the amount of drug bound. The percentage of unbound drug returned in the wash at tissue temperatures of 23.9 to 26.1 degrees C. varied from 68 to 86 per cent of the drug administered, while at tissue temperatures of 37.2 to 38.9 degrees C. only 8 to 25 per cent of the administered drug returned.

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EVALUATION OF THE CRITERIA OF OPERABILITY OF CARCINOMA OF THE BREAST

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In 1943, Haagensen and Stout (2, 3) published their criteria of operability on carcinoma of the breast. These criteria have since been modified somewhat, and the latest tabulation of the clinical criteria was published by Haagensen in 1956 (1). Patients with carcinoma of the breast are advised to have radical mastectomy except when:

1. Extensive edema of the skin over the breast is present.
2. Satellite nodules are present in the skin over the breast.
3. The carcinoma is of the inflammatory type.
4. Parasternal tumor nodules are present.
5. Proved supraclavicular metastases are present.
6. There is edema of the arm.
7. Distant metastases are demonstrated.
8. Any 2, or more of the following grave signs of locally advanced carcinoma are present: (a) ulceration of the skin, (b) edema of the skin of limited extent with less than one-third of the skin of the breast involved; (c) solid fixation of the tumor to the chest wall; (d) axillary lymph nodes of 2.5 centimeters or more in transverse diameter; (e) fixation of the axillary lymph nodes to the skin or the deep structures of the axilla.

While most of these criteria have been held valid by many surgeons when such clinical findings have been present, considerable dispute has arisen particularly over the findings listed in category 8. Some surgeons have insisted that no criteria be used to determine operability and that each patient should be individualized. Other surgeons have utilized their own criteria and have narrowed the conditions for which curative resection is denied to a bare 3 or 4 grave features.

As far as we are aware, few accounts have appeared in the literature in which large institutions have purposely tested Haagensen's criteria. One such study was published in 1949 by Tomlinson and Eckert. They found 100 cases suitable for analysis utilizing the criteria as originally published in 1943. Only 2 patients were alive and well after 5 years, and both of these patients had had cancers of the breast associated with pregnancy. It will be noted that Haagensen (1) has eliminated the condition of pregnancy and lactation in his latest tabulation of the criteria as previously listed herein.

MATERIAL AND METHODS

An analysis was made of all breast carcinomas seen at the Medical College of Virginia from 1 August 1950 to 31 December 1955. This is a consecutive series, and no cases were eliminated regardless of stage of disease or therapy employed. A total of 240 cases were thus reviewed. One of the difficulties arising from close scrutiny of the patient's chart was failure to find exact, detailed, physical findings which would enable us to classify the patient as categorically inoperable. This was particularly evident when it was attempted to evaluate 2 or more of the grave signs of locally advanced carcinoma. For example, a positive axillary node might be described as large, but a careful measurement would be lacking. Or, edema of the skin would be mentioned, but the extent of this finding rarely described. This lack of information made evaluation

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most frustrating, and it was finally decided to include patients when even only 1 grave sign was present, or when there was a reasonable chance that the patient might have been inoperable according to Haagensen.

Only 22 patients were found who had undergone radical mastectomy. A detailed analysis of these may be seen in Table I. The reader may be struck immediately by the dearth of supposedly inoperable patients treated by radical mastectomy, less than 10 per cent of the total. This observation would seem to indicate that, in general, our surgeons consciously or unconsciously were using these criteria as a guide to operability.

DISCUSSION

Only 2 patients have been lost to follow-up prior to the expiration of 5 years after radical mastectomy. Of the remaining 20 patients, 3 have survived 75 months, 77 months, and 119 months respectively.

In order to establish whether or not these 3 patients were truly inoperable by Haagensen's criteria, the charts were further scrutinized, and detailed questions asked the operating surgeon when feasible. In Patient 9 who survived 119 months, the tumor was attached to the chest wall without ulceration of the skin. Only 1 of the grave signs in category 8 was therefore present—clearly not a patient to be considered categorically inoperable. Patient 15 who survived 75 months also had only 1 grave sign, namely fixation of the tumor to the chest wall. Patient 20 who survived 77 months had a lymph node in the axilla which may have been 2.5 centimeters in diameter. It was actually stated to be between 2 and 3 centimeters in diameter. If it was the larger figure, then only 1 grave sign was present. In fact, the tumor microscopically was of the solitary circumscribed type or medullary carcinoma, a lesion known to be more favorable in its prognosis than the usual scirrhous cancer.

The remaining 17 patients failed to survive 5 years. The mean survival period was actually 20.1 months, considerably shorter than the 32.3 months reported by Haagensen and Stout and the 36.3 months reported by Tomlinson and Eckert. It is certainly possible, but not proved, that radical operation may even have hastened the death of many of our patients. In Tomlinson and Eckert's patients who were considered inoperable and treated by roentgenotherapy alone, the average survival was 34.2 months. Few would argue that Patients 1 with 2 months' survival, 6 with 6 months' survival, 7 with 4 months' survival, 11 with 8 months' survival, and 21 with 4 months' survival were not actually harmed by the operative procedure.

It is emphasized again that of these 17 nonsurvivors only 5 can be definitely classified as inoperable by Haagensen's criteria (Patients 3, 12, 18, 19, and 21). They did not necessarily represent the shortest survival periods, though Patient 21 lived only 4 months after radical mastectomy. The other 12 patients may truly have been operable, but since carefully recorded measurements of the extent of the disease in category 8 (grave signs) are lacking from the charts, this issue cannot be settled satisfactorily.

CONCLUSIONS

It would seem that our findings would support the contention that radical mastectomy is contraindicated when any one of the 8 clinical features proposed by Haagensen are present. Since the number of cases analyzed in this report is small, a plea is made for further evaluation of Haagensen's criteria of operability in large institutions where considerable breast surgery is performed. It is most essential in handling breast cancer patients that carefully documented physical findings be recorded in the charts. It is not enough to state that an axillary lymph node is large or that pigskinning of the breast is present. The node measurements must be accurate and fixation of the node to the surrounding structures carefully appreciated. If there is a

TABLE I.—SUMMARY OF DATA

Patient No. Age Race	*Duration of symptoms*	*Location of breast lesion*	*Size of breast lesion*	*Size of axillary node*	*Pathology*	*Clinical breast features suggesting inoperability*	*Treatment*	*Follow-up*
1 45 C	3 wks.	Right outer half	?	Matted nodes	Poorly diff. scirrhous, positive Rotter's, and axillary nodes	Redness over outer half of breast	Rad. mastectomy 1–7–54. Postoperative x-ray therapy	Died March 1954 (survival 2 months)
2 64 C	2 mos.	Left LOQ	9×4 cm.	?	Solitary circumscribed. Negative nodes	Peau d'orange	Rad. mastectomy 6–22–53	Pulmonary metastases 4–14–54. Died 6–18–54 (survival 12 months)
3 67 C	1 mo.	Right	8×10 cm.	4 cm.	Scirrhous mod. well diff. Positive nodes	Ulceration of skin	Rad. mastectomy 3–31–54. Postoperative x-ray therapy	Vertebral metastases 8–26–57. Died 11–11–57 (survival 44 months)
4 61 C	1 yr.	Right UOQ	8×8 cm.	?	Undiff. scirrhous	Peau d'orange	Rad. mastectomy 12–17–54	Pulmonary metastases 3–20–56. Died 8–27–56 (survival 20 months)
5 65 W	1 yr.	Entire right	?	?	Infiltrating lobular. Positive nodes	Skin ulcerated. Fixed to chest wall	Rad. mastectomy and chest wall excision 2–24–55	Died 1959 (survival 48 months approximately)
6 47 W	5 wks.	Entire left	?	Marble size	Poorly diff. scirrhous. Positive axillary and Rotter's nodes	Entire breast warm and replaced by tumor	Rad. mastectomy 12–17–51. Postoperative x-ray therapy	Died 6–23–52 (survival 6 months)
7 52 C	2 wks.	Entire right	?	?	Undiff. scirrhous. Positive axillary and Rotter's nodes	Peau d'orange	Rad. mastectomy 7–8–52. Postoperative x-ray therapy	Died 11–21–52 (survival 4 months)
8 52 C	2 wks.	Right UIQ	3×4 cm.	?	Inflammatory carcinoma. Positive nodes	Skin reddened and breast warm	Rad. mastectomy 7–20–51. Postoperative x-ray therapy	Died 1–8–54 (survival 30 months)
9 47 C	2 yrs.	Left	?	?	Poorly diff. scirrhous. Positive nodes	Attached to chest wall and skin	Rad. mastectomy 2–7–51. Postoperative x-ray therapy	No recurrence Jan. 1961 (survival 119 months)
10 48 C	6 yrs.	Right UOQ	8×4 cm.	Large	Undiff. scirrhous. Positive axillary nodes. Involvement of pectoralis major	Tumor fixed to skin	Rad. mastectomy 5–9–55	Lung metastases 11–3–58. Died 1–14–60 (survival 55 months)
11 61 W	2 yrs.	Right	Entire breast	?	Undiff. scirrhous. Extension to pectoralis major. Positive axillary nodes	Fixed to skin. Retraction of nipple. Erythema and ulceration of skin	Rad. mastectomy 5–17–54	Died 1–23–55 with generalized metastasis (survival 8 months)
12 65 C	6 mos.	Left	No definite mass	Fist size	Undiff: scirrhous. Positive axillary nodes	Peau d'orange. Ulcer of left nipple	Rad. mastectomy 3–12–55. Postoperative x-ray therapy	Liver metastasis 5–24–55. Died 12–31–55 (survival 19 months)

TABLE I.—SUMMARY OF DATA—Continued

Patient No. Age Race	*Duration of symptoms*	*Location of breast lesion*	*Size of breast lesion*	*Size of axillary node*	*Pathology*	*Clinical breast features suggesting inoperability*	*Treatment*	*Follow-up*
13 60 W	3 mos.	Right LOQ	?	?	Undiff. scirrhous. Positive axillary nodes	Peau d'orange	Rad. mastectomy 10–21–55	Lost to follow-up
14 65 C	6 mos.	Left LOQ	5×4×2 cm.	1 cm.	Poorly diff. scirrhous. Positive axillary and Rotter's nodes	Tumor fixed to chest wall	Rad. mastectomy 3–31–54. Postoperative x-ray	Died 7–31–55 (survival 16 months)
15 77 W	2 yrs.	Right UOQ	3 cm.	?	Mod. well diff. scirrhous. Positive axillary nodes	Fixed to chest wall	Rad. mastectomy 1–18–55	No recurrence 4–61 (survival 75 months)
16 65 C	6 mos.	Left UOQ	10×6 cm.	?	Undiff. scirrhous. Positive axillary nodes	Edema of skin	Rad. mastectomy 4–4–55	Died 8–9–57 (survival 28 months)
17 37 W	9 mos.	Left UOQ	3×2 cm.	3 cm.	Undiff. scirrhous. Positive Rotter's and axillary nodes	Entire breast indurated	Rad. mastectomy 9–28–53. Supraclavicular lymph node dissection 10–12–53 (nodes pathologically negative). Postoperative x-ray therapy	No recurrence 8–26–57. Subsequently lost to follow-up (survival 47 months)
18 46 C	6 mos.	Left LOQ	10×7 cm.	5×3 cm.	Undiff. scirrhous. Positive axillary nodes	Peau d'orange (slight)	Rad. mastectomy 7–8–54. Postoperative x-ray	Died 3–24–56 (survival 20 months)
19 30 W	3 yrs.	Right entire breast	9 cm.	?	Poorly diff. scirrhous. Positive axillary, Rotter's nodes, and supraclavicular lymph nodes	None in breast. Supraclavicular lymph nodes clinically involved	Rad. mastectomy 10–1–53	Died August 1954 (survival 14 months)
20 49 W	2 mos.	Right UOQ	8×8×1 cm.	2–3 cm.	Solitary circumscribed. Positive axillary nodes	Erythema of skin	Rad. mastectomy 11–12–54	No recurrence April 1961 (survival 77 months)
21 49 C	3 mos.	Left outer quadrants	?	2 cm.	Undiff. scirrhous. Positive axillary nodes	Ulceration of skin. Fixed to chest wall	Rad. mastectomy 4–2–54	Died 8–21–54 (survival 4 months)
22 40 W	1 wk.	Left UOQ	1 cm.	3 cm.	Poorly diff. scirrhous. Positive axillary nodes	None	Rad. mastectomy 6–10–55. Oophorectomy 7–16–56. Hypophysectomy 2–25–57	Recurrence in scar 7–16–56. Died 4–3–57 (survival 22 months)

difference in the clinical outcome of patients with edema of the breast of limited extent compared with those with more marked edema, only careful recording of the physical findings will ultimately enable us to appreciate these differences. It might be worthwhile to recall the final words in the 1943 paper of Haagensen and Stout (3): "We have suggested a rule for deciding the question, but we do not regard it as a definite solution. We hope that other surgeons will test the validity of our criteria of operability upon their own series of cases, and by the use of statistical methods such as we have employed add to the knowledge of the problem."

SUMMARY

1. An attempt has been made to evaluate Haagensen's clinical criteria of operability on carcinoma of the breast.

2. Two hundred and forty consecutive breast carcinomas were evaluated for this study.

3. Due to lack of well defined information in the charts, 22 patients were considered to have been definitely, or possibly, inoperable with radical mastectomy as the treatment offered.

4. Only 3 patients survived 5 years but were eliminated from discussion since further study clearly indicated that they were not inoperable.

5. The mean survival of the other 17 patients, 2 having been lost to follow-up, was 20.1 months.

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FURTHER STUDIES ON RENAL DECAPSULATION

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IN A PREVIOUS ARTICLE (2) renal autoregulation was shown to be dependent upon the presence of the kidney's relatively nondistensible capsule. The role of the renal capsule was stressed principally in relationship to renal interstitial pressure as it opposes renal arterial pressure and thus maintains an almost constant effective transmural pressure as the arterial blood pressure rises and falls. In experiments in which renal blood flow was measured during rapid massive transfusion and in other studies concerning autoperfusion of the kidneys, the distending effect of the intraluminal pressure was found to be counterbalanced by the magnitude of the ambient interstitial pressure. It appeared logical to us to regard the transmural pressure, or the gradient between intraluminal and interstitial pressure, as the important factor in the renal pressure-resistance relationship. This hypothesis appeared to be substantiated by the abolition of renal autoregulation once the kidneys were decapsulated. The convincing evidence of the importance of the renal capsule in regulating renal blood flow and its indirect action upon the systemic blood pressure prompted us to investigate further its function.

MATERIALS AND METHODS

Mongrel dogs were used. They were anesthetized by the intravenous injection of a 5 per cent solution of thiopental sodium. An endotracheal tube was inserted and 100 per cent oxygen administered by means of a mechanical respirator.

Renal blood flow was determined by a direct method which has been previously described (3). Arterial blood pressure was monitored by means of a U-tube mercury manometer connected with a plastic catheter introduced into the infrarenal aorta through a femoral artery. Esophageal temperatures were recorded by a telethermometer. The temperatures remained constant throughout the study. Renal blood flow and systemic blood pressure were observed during a 10 minute control period and at intervals following the rapid transfusion of 350 cubic centimeters of whole blood and 4 subsequent rapid transfusions of 100 cubic centimeters each. These studies were carried out in different groups of dogs from 2 to 3 days to 6 months following bilateral renal decapsulation.

In other animals, arterial inflow into the kidneys was interrupted for varying periods of time approximately 10 days following bilateral renal decapsulation. Under aseptic technique, the aorta and renal arteries were exposed and dissected free through a left extraperitoneal flank incision. The suprarenal aorta and both renal arteries were occluded for a given period of time with noncrushing vascular clamps. At the end of the period of arterial occlusion, the clamps were released, normal pulsations in the renal arteries were verified by palpation and inspection, and the wound was repaired.

RESULTS AND COMMENTS

Studies of renal blood flow and mean blood pressure. Renal blood flow and mean arterial blood pressure were studied in 51 dogs vary-

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ing in weight from 13 to 20 and averaging 15.5 kilograms. The animals were divided into 7 groups according to the time interval between bilateral renal decapsulation and the subsequent measurements of renal flow and blood pressure. Ten dogs in the first group served as controls. Ten in the second group were studied immediately after renal decapsulation, 8 in the third from 2 to 3 days, 5 in the fourth from 10 to 15 days, 4 in the fifth 1 month, 9 in the sixth 3 months, and 6 in the seventh group 6 months after decapsulation. In Figure 1 are charted the average renal blood flows and mean arterial blood pressures in the various groups before and after the 4 rapid transfusions of whole blood. In this study the average value for renal blood flow in normal control animals was of the same order of magnitude as has been found in numerous other studies which we have made. Renal blood flow in the control animals averaged 22.2 cubic centimeters per kilogram per minute. The average value was 24 cubic centimeters per kilogram per minute immediately after removal of the renal capsules and 28.8 cubic centimeters per kilogram per minute 2 to 3 days later, an increase of 30 per cent above the control level. At this time, the animal has recovered from the surgical procedure and renal capsular regeneration has not yet begun (Fig. 2). Ten to 15 days after decapsulation, the resting renal blood flow has returned to an average of 25.2 cubic centimeters per kilogram per minute or 13 per cent above the control value. At this time a thin elastic new capsular structure has developed, one which appears less rigid than the normal. A month after decapsulation the renal blood flow has returned to about the normal value, 21.6 cubic centimeters per kilogram per minute. Three months following decapsulation, at a time when the regenerated capsule is quite thick, the average renal blood flow is approximately 14 per cent less than the control value, 19.3 cubic centimeters per kilogram per minute. Six months following decapsulation, when the capsule is quite thick and inelastic, the renal blood flow is still less, 18.3 cubic centimeters per kilogram per minute, or 18 per cent less than the control. Since, in spite of individual variations, the average values of renal blood flow in normal dogs from one study to another have been so nearly constant, variations which have been observed in the present groups of dogs at different periods following decapsulation are regarded as significant changes.

The mean resting arterial blood pressure was found to be on the average less than normal or within the normal range in those animals studied immediately, 2 to 3 days, 10 to 15 days, and 1 month following decapsulation. In the control animals, the average mean arterial pressure was 140. In those animals studied 1 month or less following decapsulation, this value on the average ranged between 120 and 140 millimeters of mercury. The mean systemic arterial pressure was definitely, though moderately, elevated in those animals studied 3 and 6 months following decapsulation, ranging between 150 and 160 millimeters of mercury. Early after decapsulation the mean arterial pressure tended to be somewhat lower than normal and the renal blood flow higher. With an increasing lapse of time subsequent to decapsulation these values had a tendency to diverge, the renal blood flow falling and the arterial blood pressure rising.

A similar difference in response of arterial blood pressure and renal blood flow to rapid transfusions was observed early and late after renal decapsulation. In the control animals transfusion evoked a marked rise in systemic arterial pressure and a trivial increase in renal blood flow. On the contrary, immediately after decapsulation the blood pressure increased only about 6 per cent in response to transfusion, while the renal blood flow increased approximately 62 per cent. A few days later transfusions brought about a similar trivial increase in blood pressure and a 35 per cent increase in renal blood flow. Since, in this group, the pretransfusion value of renal flow was 30

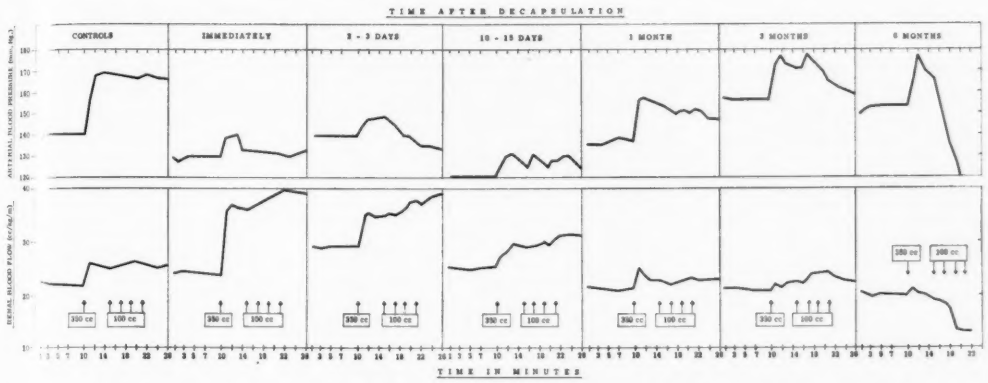

FIG. 1. Chart showing response of mean arterial blood pressure and renal blood flow to rapid transfusions in control dogs and in animals studied at varying periods following renal decapsulation. The mean drop in arterial pressure during the later transfusions 3 and 6 months after decapsulation results from the fact that certain animals tolerated the transfusions poorly and expired.

per cent higher than in the preceding group, the absolute value of renal flow after transfusion was about the same in the two. In the groups studied from 10 to 15 days, 1 month, 3 months, and 6 months after decapsulation, the average rise in systemic arterial pressure following transfusions was 11, 15, 14, and 17 per cent respectively. In the same groups, the increase in the renal blood flow was 24, 17, 16, and 7 per cent respectively.

It is of especial interest that the regenerated renal capsule 1 month following decapsulation was found grossly and microscopically to be similar to the normal renal capsule in view of the fact that at this period the dogs' response of blood pressure and renal blood flow to transfusion was quite like that of those in the control group. Indeed, those animals studied a month after decapsulation had approximately the same resting blood pressure and renal blood flow values as did the normal controls. At earlier periods following decapsulation, the resting renal blood flow tended to be higher and the systemic pressure lower than normal. Groups studied later after decapsulation tended to be hypertensive.

Normal animals and those transfused 1 month or earlier after decapsulation withstood the transfusions without difficulty. After transfusion, however, 35 per cent of those studied 3 months after decapsulation and 50 per cent of those studied 6 months after decapsulation died.

Arterial inflow into the kidneys was interrupted for varying periods of time in 30 animals subjected about 10 days previously to bilateral renal decapsulation. The arterial inflow was excluded for 1 hour in 10 animals. One of them died the day following the study and 2 others in from 5 to 8 days. The 3 animals which died showed signs of tubular necrosis of the kidneys. The vascular tree and the glomeruli were essentially intact. In 20 dogs, renal arterial inflow was excluded for 2½ hours. One died almost immediately and the other 19 in from 3 to 15 days. Their kidneys showed massive necrosis. The necrosis involved all segments of the renal structure. Similar experiments in normal dogs (3) have shown that exclusion of circulation from the kidneys for 1 hour results in no death and that exclusion of arterial inflow for 2½ hours results in an 80 per cent mortality.

DISCUSSION

In 1902 Albarran and Bernard reported before the Paris Biological Society that rapid regeneration of a capsular structure occurs about decapsulated kidneys. Rolnick

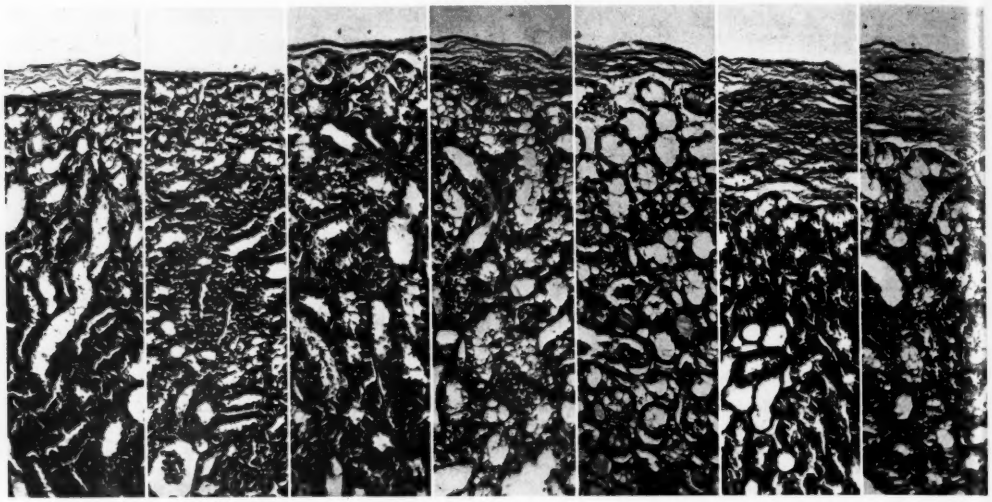

FIG. 2. Photomicrographs showing from left to right cross sections of the outer portion of the kidney in normal dogs and in animals immediately, 2 to 3 days, 10 to 15 days, 1 month, 3 months, and 6 months after decapsulation.

demonstrated formation of the new capsule by from the seventh to the tenth day. Capsular regeneration was judged to be complete by the third week and the regenerated capsule was noted to become increasingly thick during the next 2 months. The new capsule had no elasticity and was firmly attached to and infiltrated the cortex. In our experiments, both direct gross observation and microscopic study reveal evidence of capsular regeneration beginning as soon as 4 to 5 days after decapsulation. The new capsular structure gradually increases in thickness until the end of the second month. From the third month to the sixth, no further increase in thickness is observed. At this period, however, the loss of elasticity is almost complete. By the end of the sixth month the new capsule is an inelastic hull firmly encasing the kidney. No particular changes in the size or appearance of the kidney itself are noted.

These progressive changes in the physical structure of the new capsule have given us the opportunity to investigate renal blood flow and blood pressure and the response of both to massive transfusions with varying degrees of capsular rigidity. In the early stages when the new capsule is thin and distensible, renal blood flow increases with transfusion of blood while systemic blood pressure rises only slightly. The response differs as the capsule loses its elasticity. One month following decapsulation, when the regenerated capsule grossly and microscopically resembles the normal, the response of blood pressure and renal blood flow to transfusion is identically the same as in normal animals. Three months and 6 months after decapsulation, when the capsule is more inelastic, the animals are hypertensive and withstand transfusion badly. The mortality following transfusions is 35 per cent in the first and 50 per cent in the second group. Both groups respond with a rise in blood pressure and with little or no increase in renal blood flow.

It is appropriate to mention the observation made by Swann and his associates during the course of study of perinephritic hypertension produced by encasing the kidney in a cellophane bag. By relating interstitial renal pressure in control dogs at varying levels of blood pressure with interstitial

renal pressure in perinephritic dogs at the same levels of systemic pressure, they found that the interstitial renal pressure in the perinephritic dogs rises one-third faster in response to an increase in blood pressure than it does in the normal animal. Waugh and Hamilton studied the renal arterial pressure in animals in which the kidney was encased in a pressure chamber and demonstrated that the kidney became smaller and its capsule more flaccid as the ambient pressure in the chamber was increased. He concluded that the gradient between the renal arterial pressure and the renal interstitial pressure diminished as the ambient chamber pressure was increased. Such observations and the experiments we are reporting tend to make logical the assumption that the pressure gradient between renal arterial and interstitial renal pressure is the most important factor in renal pressure-resistance relationship.

In our dogs, arterial hypertension was observed a few months after decapsulation, at the time when renal blood flow was slightly below normal. This increase in blood pressure is undoubtedly related to that which appears after induction of perinephritic scarring. In both of the instances, the kidney is surrounded by a stiff fibrotic hull.

The effect of renal decapsulation upon renal hemodynamics is demonstrated by the average pretransfusion values of renal blood flow observed at varying periods following decapsulation. The greatest increase in the resting renal blood flow is observed 2 to 3 days after decapsulation at a time when the animal has recovered from the operative procedure and has no visible capsular regeneration. At this time there is a 30 per cent increase in the resting renal blood flow as compared with the control animals. Schneider and Wildbolz reported a 20 per cent increase in renal blood flow following decapsulation. As the renal capsule regenerates and becomes thicker and more inelastic, the resting values for renal blood flow decrease.

Our experiments demonstrate that animals previously subjected to renal decapsulation withstand a period of interruption of arterial inflow to the kidneys more poorly than do normal dogs. The higher mortality may well be related to the paucity of collateral circulation through the capsule. This would be in agreement with Harrington's observations. He found that the regenerated capsule 17 days following decapsulation contained fewer blood vessels than the normal. Myers and Hunter observed in rabbits a fibroplastic proliferation over the denuded cortical surface but no new blood vessel formation.

SUMMARY

Within a few days after renal decapsulation in the dog, capsular regeneration begins. By 1 month it closely resembles the normal structure both grossly and microscopically. Before this time it is more distensible and afterward thicker and more inelastic. One month after decapsulation resting renal blood flows and mean arterial blood pressure are about normal, and the response of both to rapid transfusions is normal, that is, a rise in blood pressure with little change in renal blood flow. Earlier the resting renal blood flows are somewhat elevated and blood pressure is normal or reduced. Transfusions tend to increase renal flow and to change pressure little. Later the blood pressure is elevated and the renal blood flow reduced. The pressure rises and the renal flow is little affected by transfusions. Transfusions are poorly tolerated in these groups. Approximately 10 days following decapsulation, animals tolerate periods of renal arterial exclusion more poorly than do normal dogs, probably because of decreased collateral blood supply. The significance of these observations is discussed.

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IMMEDIATE AND REMOTE SEQUELAE IN TRAUMATIC DIAPHRAGMATIC HERNIA

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THE MANAGEMENT of trauma occupies an increasingly conspicuous role in civilian surgical practice. In 1958, an estimated 9,100,000 accidental injuries with 91,000 subsequent deaths occurred in the United States. In automotive accidents, injuries of the head and lower extremity were observed most frequently in multiple body injuries. The more obvious trauma is readily recognized; other less apparent injuries may remain obscure for periods ranging from hours to years. In this latter category, a prominent entity is traumatic diaphragmatic hernia in which abdominal viscera have entered the pleural, or more rarely the pericardial, cavity. Certain patterns of injury are found with sufficient frequency to suggest involvement of the diaphragm.

This study was undertaken for the following reasons: (1) to discover the factors responsible for allowing traumatic diaphragmatic hernias to remain occult; (2) to review the manner in which these lesions may masquerade as another disease; and (3) to establish principles upon which early diagnosis and management can be based.

The records of all patients with traumatic diaphragmatic hernia admitted to the University of California Medical Center, San Francisco, and the University of California Service of the San Francisco General Hospital between 1937 and 1959 were reviewed. The criteria used for the diagnosis of traumatic diaphragmatic hernia were that no true hernial sac was present and that one or more of the abdominal organs protruded, or potentially protruded, through the diaphragmatic rent into the thorax. Twenty-five cases met these criteria.

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The injuries which produced dehiscence of the diaphragm were of two types: (1) those due to the direct force of penetrating wounds (direct type) and (2) those due to the force which did not penetrate the thorax or abdomen and thus only in an indirect fashion traumatized the diaphragm (indirect type). Patients with direct trauma to the diaphragm have a somewhat better prognosis than those with indirect trauma. The latter group being more frequently handicapped with serious concommitant injuries.

The indirect type of injury accounted for 20 of the 25 cases in this series. The majority of these injuries were due to crushing and high velocity impact forces such as automobile accidents and falls from various heights. The remainder were caused by miscellaneous trauma recorded as "a kick in the abdomen by a horse," and by "a trailer falling on the shoulders of an elderly man forcing him into the jack knife position." In other instances, the injury was less exact or was described as "due to football injury" or "occurred while playing games." One patient recalled a "twisting motion" while washing a window as the only possible trauma which caused a rupture of the left hemidiaphragm. In 2 instances the patient could not remember a specific injury.

Direct trauma was responsible for rupture of the diaphragm in 5 patients; 3 of these were due to gunshot wounds and 2 were caused by stab wounds with long-bladed knives. In cases in which the wound of entry was near the anatomic level of the diaphragm, penetration of some portion of it

was automatically suspected. It must be remembered, however, that the direction of the missile or blade is important since high wounds of entrance are able to injure the diaphragm if the pathway is downward. The upward projection of abdominal wounds should be viewed with similar suspicion. Also, the dome of the diaphragm rises to a high point in the thorax in the squatting and flexed positions with extreme expiration. In 1 of our patients the diaphragm was torn by a bullet which entered the left third intercostal space in the parasternal line.

The left side of the diaphragm was involved in 23 patients and the right side in 2.

Operations were performed in 22 of the 25 patients.

CLINICAL COURSE

A remarkably constant series of events follows a traumatic rupture of the diaphragm. This sequence, which consists of both immediate and remote sequelae, has been noted by Carter and Guiseffi. It can be divided into three phases. The initial or acute phase begins with the original trauma and terminates with the apparent recovery from the injury. It is during this phase when attention is directed toward the care of other injuries that the diaphragmatic rent is likely to remain undetected. In this series of 25 cases, an acute rupture of the diaphragm was recognized during the initial phase on only 6 occasions, as exemplified by the case of a 52 year old colored male who was stabbed in the chest 7½ hours before admission into the hospital. The wound of entrance was made with a butcher knife. It was located in the left eighth intercostal space at the posterior axillary line. A tube thoracostomy was performed on the second hospital day for hemothorax on the left side. Roentgenogram of the chest revealed "elevation of the left hemidiaphragm." On the third hospital day, left shoulder pain occurred. Roentgenogram of the chest now disclosed "gastric dilatation." A left exploratory thoracotomy was performed on the fifth hospital day. There was a transverse incision 7 centimeters long in the tendinous portion of the hemidiaphragm. The stomach and part of the gastrohepatic and greater omenta were in the left pleural cavity. The abdominal viscera were reduced from the chest to the abdomen, the rent was repaired, and the patient made an uneventful recovery.

The latent phase is one of variable length. The patient is relatively free from incapacitating symptoms even though a rupture has occurred and has been overlooked during the initial phase. The duration of the latent period varies enormously. The longest in our series was 27 years. During this interval the patient is often distressed by symptoms referable to the epigastrium and left upper portion of the abdomen. These symptomatic episodes are usually of limited duration and are probably due to intermittent incarceration of the herniated viscera. The diagnosis of traumatic diaphragmatic hernia was made in 15 of our cases during the latent phase, as in the case of a 41 year old male who, at the age of 18, had been kicked in the midepigastrium by a horse. He recovered fully after several days and remained well until the age of 40 when intermittent midepigastric colicky pain developed. Physical examination revealed diminished expansion, dullness to percussion, and absent breath sounds in the left lower hemithorax. The heart was shifted to the right.

In January 1941, a transabdominal repair of the traumatic diaphragmatic hernia was accomplished. The stomach, transverse colon, spleen, and part of the small intestine were found in the left pleural cavity protruding through an oblique tear across the full length of the left hemidiaphragm. The abdominal viscera were returned to the peritoneal cavity. The partially atelectatic left lung was re-expanded, and the diaphragmatic rent was successfully repaired.

The obstructive phase may occur at any time to terminate the latent phase. The incarcerated viscera become obstructed, leading to congestion, strangulation, and necrosis if the condition is not promptly relieved. Four of the 25 cases, herein re-

ported, fell into this classification, as illustrated by the case of a 61 year old white male who was struck on both shoulders by a trailer which tipped over and forcibly pinned him down momentarily. He experienced a tearing pain in the left epigastrium, and nausea and vomiting soon developed. All symptoms abated within half an hour and he recovered completely in a few days. Eighteen months later he became acutely ill with diffuse abdominal pain, nausea and vomiting, abdominal distention, and obstipation.

Physical examination disclosed limitation of motion, tympany to percussion, and borborygmus in the left lower portion of the chest.

Repair was successfully accomplished through an abdominal approach. The ascending colon, the proximal part of the transverse colon, as well as several loops of ileum were distended. Two loops of distal transverse colon and the greater omentum were incarcerated in the left pleural cavity and were obstructed by a small rent in the midportion of the left hemidiaphragm. The abdominal viscera were delivered from the left pleural cavity with some difficulty because of the presence of firm adhesions.

During the initial phase it may be difficult to obtain an accurate history in the face of multiple injuries, shock, or unconsciousness. Perseverance in learning the mechanics of injury, such as the direction of flight of the inflictive missile in relation to body position, may alert one to the possibility of diaphragmatic injury. Also the injury need not necessarily be severe to produce a tear in the diaphragm. A careful inquiry into past injuries is often most revealing in discovering traumatic hernias during the latent or obstructive phases.

Symptoms are related to the space occupying effects of the abdominal viscera entering through the torn hemidiaphragm into the pleural cavity. They are modified only by the degree of intrusion and obstruction.

During the initial phase, herniation of viscera may not be sufficiently established to cause symptoms; concomitant problems are likely to overshadow any that are present. In such circumstances the diagnosis of traumatic diaphragmatic hernia may not even be considered. Suggestive symptoms are pain in the left upper portion of the abdomen, in the left lower part of the thorax, and in the left shoulder region.

Gastrointestinal symptoms became prominent during the latent phase. In the present series, pain was most frequently located in the epigastrium and was described as intermittent and cramplike. Occasionally, pain was noted in the left shoulder, paraumbilical region, rectum, and testicles. The most common radiation was into the left lower portion of the thorax. A heavy meal often initiated or increased the distress. Posture influenced the character of the painful attacks. The pain was frequently aggravated by lying supine or upon the left side. The discomfort was often relieved by assuming the standing position or by lying on the right side. Relief was also afforded by expelling gas via the esophagus or colon, resulting in the deflation of incarcerated viscera. Tarry stools were the result of vascular congestion which produced bleeding into the stomach, small bowel, or colon. Shortness of breath on exertion, cough, hemoptysis, and palpitation were due to the effects of compression upon the cardiorespiratory apparatus.

In the obstructive phase, the distribution of pain was similar to that noted in the latent phase but of greater severity. The patients appeared much more seriously ill. Obstipation was marked. Nausea and vomiting were pronounced, so that a diagnosis of intestinal obstruction was immediately considered (Table I).

Early in the initial phase, before any of the abdominal viscera have penetrated deep into the pleural cavity, the physical signs are usually obscure. Once the hernia is established, diminished respiratory excursion of the left lower portion of the thorax, dullness or tympany to percussion, diminished to absent breath sounds, borborygmus, and displacement of the area of cardiac dullness to the right may be present.

TABLE I.—SYMPTOM ANALYSIS FROM 23 CASES OF TRAUMATIC LEFT HEMIDIAPHRAGMATIC HERNIA

Pain	
Abdominal	19
Left side of chest	8
Left shoulder	5
Aggravated by meals	8
Aggravated by position	6
Relieved by position	5
Relieved by enema or cathartics	2
Testicular pain	2
Rectal pain	1
Left arm	1
Aggravated by respiration	1
Nausea and vomiting	9
Shortness of breath on exertion	5
Excessive belching and flatulence	4
Noises in left side of chest	3
Obstipation	3
Melena	2
Hematemesis	1
Hemoptysis	1
Cough	1
Palpitation and tachycardia on exertion	1

In the initial phase, associated injuries may detract from the subtler signs of diaphragmatic injury. The presence of cyanosis and dyspnea may require unusual diagnostic skill to distinguish between a left-sided tension pneumothorax and a dilated stomach in the left pleural cavity. Subcutaneous emphysema or the bony crepitus from fractured ribs may be the only external signs of an injury sufficient to rupture the diaphragm. The location of external wounds of the chest and abdomen should call to mind that a mobile diaphragm might have been in the path of the missile.

During the latent phase, when the patient has more or less become adjusted to the presence of abdominal viscera in the pleural cavity, abnormal physical findings in the left lower portion of the thorax suggest the diagnosis. In the present series, the most frequent signs were dullness and diminished breath sounds in that area.

The obstructive phase is characterized by signs of high or low gastrointestinal obstruction, depending on whether the stomach, colon, or both are obstructed. Although in gastric obstruction the abdomen may appear normal, it is usually distended in those cases in which the colon is primarily involved. However, if most of the abdominal viscera are in the thorax during colonic obstruction, the abdomen may be deceptively flat (Table II).

CONCOMITANT INJURIES

Indirect or nonpenetrating trauma accounted for the majority of concomitant injuries. Most of the soft tissue injuries as well as the fractures of the ribs and extremities occurred on the left side of the body. This afforded a clue to possible rupture of the left hemidiaphragm.

Carlson and his associates directed attention to fractures of the pelvis and lumbar vertebrae in association with dehiscence of the diaphragm. In a study of nonpenetrating wounds of the chest and abdomen, they found that 6 of 9 patients had concomitant fractures of the pelvis or lumbar vertebrae or both. In the present series of 20 cases due to indirect trauma, 4 pelvic fractures were found, but there were no vertebral fractures. It is possible that in some of the accidents which occurred years previously, unrecognized osseous injury may have been sustained.

Trauma in the group of patients with direct wounding of the diaphragm was limited to the path of the missile. The most serious of the associated injuries were the lacerations of the lung, spleen, and liver. Hemothorax resulted on 2 occasions, and in 1 of these it progressed to empyema (Table III).

ROENTGENOLOGIC FINDINGS

Early in the initial phase, the roentgenogram of the chest may not suggest diaphragmatic involvement. Serial films obtained during the first week may reveal an unidentified shadow above the left hemidiaphragm that may progress to a picture compatible with the presence of an abdominal viscus in the pleural cavity (Fig. 1a and b). The utilization of repeated roentgenograms of the chest is an established aid in demonstrating a suspected diaphragmatic hernia.

The use of a nasogastric tube will clarify otherwise obscure findings if the tube can be seen in the stomach above the expected

TABLE II.—ANALYSIS BY PHASE OF PHYSICAL SIGNS

Initial phase—5 cases	
Decreased breath sounds left lower part of chest	3
Unconsciousness	2
Cyanosis	2
Dyspnea	2
Crepitus left side of chest	2
Subcutaneous emphysema	1
Shock	1
Heart shifted to right	1
Dullness to percussion left lower part of chest	1
Decreased mobility left lower part of chest	1
Shotgun wound left hypochondrium and lower part of chest	1
Stab wound left 8th intercostal space post. axillary line	1
Latent phase—14 cases	
Decreased mobility and impaired resonance left lung base	14
Borborygmus left side of chest	8
Heart shifted to right	1
Tympany left side of chest	1
Trachea to left	1
Scar left 7th intercostal space midaxillary line	1
Obstructive phase—4 cases	
Distended abdomen	2
Decreased mobility, impaired resonance left lung base	2
Loops small bowel ladder pattern	1
Borborygmus left side of chest	1
High pitched abdominal peristalsis	1
Midabdominal rigidity	1
Scar left 8th intercostal space ant. acillary line	1
Scar left 3rd intercostal space parasternal line	1
Scar left 9th intercostal space ant. axillary line	1

From 23 cases of left hemidiaphragmatic hernia

TABLE III.—CONCOMITANT INJURIES

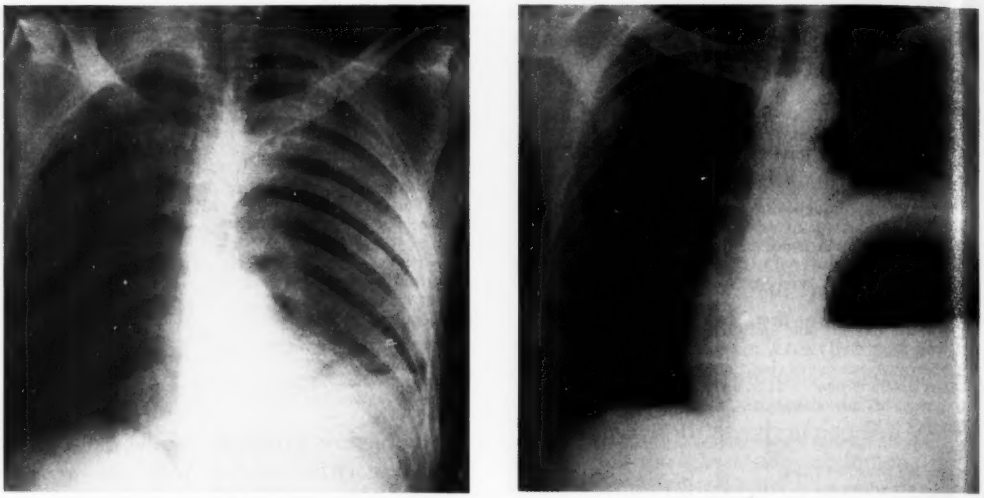
Indirect trauma—20 cases	
Fractures	
Ribs, left	8
Pelvis	4
Tibia, left	2
Fibula, left	2
Radius, left	2
Ulna, left	1
Tibia, right	1
Fibula, right	1
Dislocation shoulder, right	1
Dislocation great toe, right	1
Bladder rupture	1
Internal iliac artery rupture, right	1
Cerebral contusion	2
Direct trauma—5 cases	
Splenic injury	2
Hemothorax, left	2
Lung laceration, left	1
Liver laceration	1

level of the hemidiaphragm. Fluoroscopy may be misleading. The arched shadow above the gastric air bubble will resemble the hemidiaphragm, although it is actually the wall of the stomach protruding through the dehiscence. Eventration of the diaphragm is often erroneously diagnosed from the fluoroscopic findings. Occasionally, the distended stomach in the left pleural cavity will give the appearance of a tension pneumothorax.

Delineation of a herniated viscus is readily accomplished by oral or rectal administration of radiopaque solution. If the column of barium is halted at the cardioesophageal junction, one can infer that the stomach has herniated into the left pleural cavity, producing an acute angle obstruction. If the contrast medium is able to negotiate this acute angle, the stomach will be visualized in the left pleural cavity. Further, if the barium passes into the duodenum, the gastroduodenal and cardioesophageal junctions will be noted to lie in close proximity. The entire picture produces a reversal of the normal gastric position with the greater curvature resting superiorly and the lesser curvature inferiorly (Fig. 2).

The splenic flexure and adjacent portions of the descending and transverse colon may find their way into the left hemithorax. Accordingly, the barium enema may reveal one of several patterns. It may stop in the descending colon below the splenic flexure because of complete occlusion by the edges of the torn hemidiaphragm at this level. A small amount of barium may slip by the constriction to appear as a series of small lakes in the left side of the chest (Fig. 3). The barium may flow uninterruptedly from the descending colon through the splenic flexure in the left hemithorax and continue on into the transverse colon below the torn hemidiaphragm.

The roentgenograms of the chest in the latent phase commonly cause confusion. During this period the patient manifests minimal or no symptoms, yet there may be slight haziness above what appears to be the hemidiaphragm. A homogenous density of the left lower portion of the chest and displacement of the cardiac shadow to the right occasionally are present (Fig. 4). The appearance of air cysts and multiple areas of fluid loculation give the impression of primary lesions of the pulmonary parenchyma or pleural space instead of herniated abdominal viscera (Fig. 5).



a b

FIG. 1. Illustrating the value of serial roentgenograms taken 24 hours apart. a, The obscure shadow in the region of the left hemidiaphragm visible on 22 November 1957 was replaced by, b, a herniated stomach on 23 November 1957.

Roentgenographic studies of a right traumatic hernia are quite different from those on the left. There may be a nodular or mushroom projection into the right pleural cavity, representing a portion of the liver. This picture simulates a mediastinal, pulmonary, or diaphragmatic tumor. Pleuropulmonary amebiasis may be confused roentgenographically with a herniated liver which has passed through a traumatic rent in the right hemidiaphragm. A diagnostic pneumoperitoneum will usually clarify the issue. If the hernia is large, a homogenous density may obscure the right lower hemithorax. A contrast enema will reveal a high lying hepatic flexure which has moved superiorly with the liver. The presence of healed fractured ribs with a density at the lower part of the hemithorax is very suggestive of previous diaphragmatic injury. However, fractured ribs need not necessarily accompany traumatic diaphragmatic hernia.

During the initial phase, the conditions most commonly misdiagnosed as traumatic hernia of the left hemidiaphragm were gastric dilatation and eventration of the diaphragm due to misinterpretation of fluoroscopic findings and the chest roentgenograms. Studies with the use of opaque media facilitated the diagnosis when these maneuvers were undertaken.

In the latent phase, erroneous diagnoses were atelectasis, pneumothorax, pneumonia, bronchogenic carcinoma, and tuberculosis. The latter diagnoses again stemmed from misinterpretation of the plain roentgenogram of the chest.

TRAUMATIC HERNIA OF THE RIGHT HEMIDIAPHRAGM

Only 2 of the 25 patients experienced rupture of the right hemidiaphragm. In 1 instance this was diagnosed in the initial phase and in the other in the latent phase. In both instances rupture was due to indirect trauma.

The patient treated in the initial phase had such severe concomitant injuries that he died shortly after injury. The second patient is of special interest because 12 years elapsed between the accident and the onset of symptoms. At operation, the right half of the colon, the cecum, appendix, small bowel, proximal part of the duodenum, right kid-

ney, and right lobe of the liver were found in the pleural cavity.

MECHANISM OF PRODUCTION OF TRAUMATIC DIAPHRAGMATIC HERNIA

The diaphragm is constantly subjected to the stress of a difference in pressure between the abdomen and thorax. As the diaphragm descends in inspiration, the pressure above is reduced while that below is increased. The resultant increase in the pleuroperitoneal pressure gradient tends to thrust the diaphragm upward.

Marchand has shown that, during quiet breathing in the supine position, the average intraperitoneal pressure varies from +2 to +10 centimeters of water. The corresponding intrapleural pressures vary from −5 centimeters during expiration to −10 centimeters during inspiration. Thus, the pleuroperitoneal pressure gradient during quiet respiration varies between 7 and 20 centimeters of water pressure. With maximum inspiratory effort the pleuroperitoneal gradient may exceed 100 centimeters of water pressure. During coughing, both the intrapleural and intraperitoneal pressures become positive so the pressure differential between the two cavities is not markedly increased.

Intraperitoneal pressures of 100 centimeters of water may be produced during the Valsalva maneuver. This upward pressure on the diaphragm is counteracted by the simultaneous increase of the intrathoracic pressure. During this maneuver a pleuroperitoneal pressure gradient of approximately 30 centimeters of water is produced which is considerably less than that resulting from deep inspiration. Any force, such as indirect trauma, which increases the pleuroperitoneal pressure gradient will tend to thrust the diaphragm superiorly. This resulting stress will be most evident on the less buffered portions of the diaphragm. The protective function of the liver and kidney upon the right hemidiaphragm is well documented by the low incidence of traumatic lacerations in this region. The

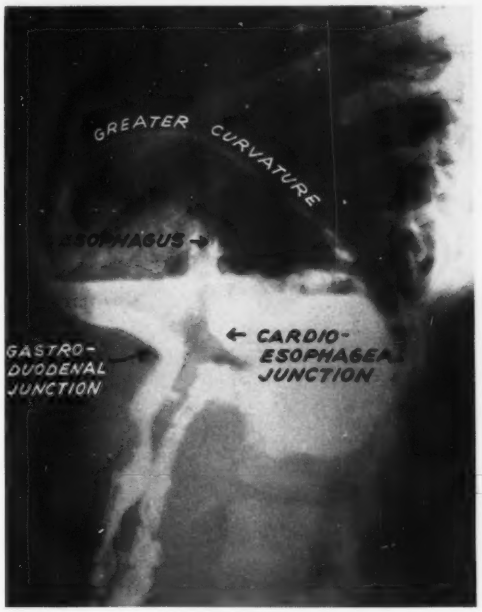


FIG. 2. Complete herniation of the stomach into the left pleural cavity. The cardioesophageal and gastroduodenal junctions are in close proximity.

left lobe of the liver, the stomach, spleen, and left kidney afford a less bulky and more mobile buffering force to the under surface of the left hemidiaphragm.

Buffering action above the diaphragm, which tends to reduce the pleuroperitoneal pressure gradient, is produced by the heart and the pericardium attached to the central tendon, as well as the base of the lungs molded to the superior surface of the diaphragm. The magnitude of the buffering force of the lungs will vary directly with the pressure of the air contained within them. Maintenance of this intrapulmonic pressure will depend upon whether the glottis is open or closed.

Certain ligamentous attachments of the abdominal viscera beneath the diaphragm —the left and right triangular, falciform, phrenicolienal, lienorenal, gastrolienal, and gastrohepatic ligaments—limit but do not preclude the sliding motion of positional changes which allows a changing buffering

FIG. 3. Herniated distal part of transverse colon in the left pleural cavity appearing as small lakes of barium (arrows). The proximal parts of the transverse and the ascending colon are distended with gas.

action. Hence the resistance to external trauma is obviously weakest beneath the left hemidiaphragm. The point of minimal buffering area will shift with the direction and location of the impact in relation to the position of the patient. This may in part explain the variable locations of the diaphragmatic rents which do not seem to follow any particular pattern (Fig. 6).

The force of indirect trauma increases the intraperitoneal pressure. It rapidly outstrips the intrathoracic pressure and produces a large pleuroperitoneal pressure gradient. This explosive force tears the diaphragm at the point of minimal buffering resistance. If this tear is large, abdominal viscera immediately enter the pleural cavity. If it is small, it may be temporarily occluded by the omentum, spleen, or liver. If the patient has a diaphragmatic laceration which is occluded and thereby escapes detection, the tendency will be for the abdominal viscera to wedge their way slowly through the rent. A sudden increase in the pleuroperitoneal pressure gradient may hasten this process. Coaptation with healing of the edges of the laceration becomes impossible under these circumstances. As the herniated parts insinuate themselves further into the hemithorax, the threat of obstruction and strangulation increases, although this may not take place for many years. Persistent increasing obstruction proceeds to strangulation, gangrene, and thoracogastric fistula.

The organs most frequent to herniate into the left pleural cavity were the stomach, greater omentum, colon, spleen, and small bowel in varying combinations. On the right side, the hollow viscera seemed to follow the progress of the liver and kidney into the chest (Table IV).

THERAPY

Once the diagnosis of traumatic diaphragmatic hernia has been established, operative repair should be undertaken without further delay. Exceptions depend upon individualization of cases as, for example, a debilitated patient in the latent phase in whom the risk of surgery would be prohibitive. Three patients had an established diagnosis of traumatic herniation through the left hemidiaphragm, but operation was not performed. Their concomitant fractures were completely and thoroughly treated, but the seriousness of the diaphragmatic injury was not recognized. Two of these patients were discharged with adequate notes about the fractures, but no comments were made about the diaphragmatic lesion, indicating that those in attendance were not aware of its presence. The third patient was treated on an outpatient basis for a Colles' fracture. Four years later she returned because a miniature roentgenogram of the chest showed a lesion at the base of the left lung. A correct diagnosis was then made but no repair was undertaken because of her age—74 years—and associated infirmities. Per-

haps the gravity of the sequelae of this lesion was not appreciated.

The reparative problems are somewhat different in the three phases. Concomitant injuries in the acute stage may delay the hernia repair in favor of closure of a ruptured viscus, control of hemorrhage, or management of a compound fracture. However, if such a hernia is recognized in the initial stage, its repair should not be delayed unnecessarily long. The diaphragm can often be repaired along with the management of concomitant injuries.

It is important to recognize that a distended stomach in the left pleural cavity is able to mimic the signs and symptoms of hemorrhage because of mediastinal compression. Even in a recently injured patient who presents evidence of deterioration, an operation to relieve mediastinal displacement may be lifesaving. This is especially true of the injured patient whose blood loss is adequately replaced and whose concomitant injuries are not of sufficient severity to account for deterioration. The large herniated gastric pouch when filled with air easily suggests a tension pneumothorax. Before a trocar is introduced into the left side of the chest, this possibility should be carefully considered.

In the current series, the ruptured hemidiaphragm was approached through the abdomen in 11 cases. Two of these patients were operated upon during the initial phase, 7 during the latent phase, and 2 during the obstructive phase. The transabdominal approach created a number of technical difficulties due to inadequate exposure. In 3 instances it was necessary to enlarge the abdominal incision by a lateral extension in order to gain sufficient exposure for repair. On 1 occasion the diaphragmatic repair through the abdomen was unsatisfactory so that the recurrence of the hernia was repaired transthoracically at a later date.

One of the most troublesome technical problems was the presence of adhesions in the pleural cavity which bound the abdominal viscera to surrounding structures. This feature made delivery of the herniated contents from the pleural into the peritoneal cavity difficult when the procedure was performed via the abdominal route. The spleen was torn in 3 cases, and splenectomy was necessary in 1 instance. On 2 occasions it was necessary to extend the abdominal incision across the costal margin into the pleural cavity to gain adequate exposure. Twice, the abdomen was opened and then closed in favor of a later thoracotomy. One of these cases occurred during the obstructive phase and a decompressing cecostomy was performed.

FIG. 4. Herniated splenic flexure of colon, omentum, spleen, and tail of pancreas casting a dense shadow in the left lower part of the chest and displacing the heart to the right.

Of the 9 operations performed purely through the thorax no technical difficulty of note was encountered. Two of these patients were operated upon during the initial phase, 6 during the latent phase, and 1 during the obstructive phase. Adhesions between the herniated viscera and the thoracic contents were quite easily separated. Adhesions which had occurred in the left

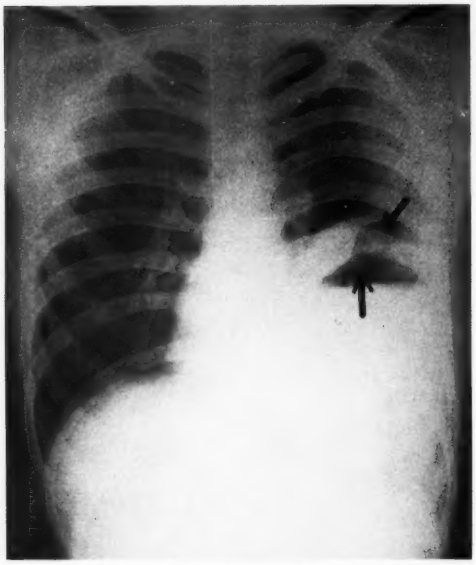


FIG. 5. Herniated stomach, omentum, jejunum, and spleen appearing as air cysts and loculated fluid (arrows) in left lower hemithorax.

upper quadrant of the abdomen were easily managed through the diaphragmatic rent. The technical case of the thoracic approach recommends its use whenever possible.

The surgical repair of the defect was executed with nonabsorbable sutures, silk or cotton, in all cases. Simple closure was performed in 15 cases and closure by imbrication in 4. In 3 cases, the edge of the laceration was sutured to intercostal muscle.

RESULTS

Six of the 22 patients who underwent repair were followed up for periods of 1 to 11 years. The remainder were lost for recording purposes within a year after operation. One patient who died from coronary thrombosis 5 years after simple repair of the diaphragmatic defect had an intact diaphragm at postmortem examination. Another patient underwent a gastric resection 11 years after repair of a large right hemidiaphragmatic hernia by simple closure. The hernia repair was found to be intact at the second operation. A third patient whose defect was closed by imbrication has been observed for 8 years with no evidence of recurrence. There have been no known recurrences in this series following a satisfactory repair by imbrication or simple closure. The two methods seem to have equal merit in the repair of diaphragmatic rents.

Three of the 22 patients died in the early postoperative period. Severe cerebral contusion accounted for one death and unrecognized rupture of the right internal iliac artery accounted for another. The third patient expired after an abdominothoracic operation to repair a traumatic hernia of the left hemidiaphragm. The spleen as well as the other herniated organs was fixed in the thorax by adhesions. During delivery of the stomach and the left half of the colon, the appendix was damaged and was therefore removed. This patient died on the fifth postoperative day from pneumococcal and Escherichia coli bacteremia, empyema, and adrenal insufficiency.

DISCUSSION

Impact injuries resulting from increased vehicular speed of traffic have increased the incidence of traumatic diaphragmatic hernia. We may still expect to encounter these lesions in the latent and obstructive phase because of the difficulties in diagnosis during the initial phase.

The three phases of this condition have been generally appreciated only recently. However, the astounding French surgeon of the 16th century, Ambroise Paré (6), clearly described a case that passed through the three phases, "A Captain . . . received a gunshot wound, the ball entering at the end of the sternum near the ensiform cartilage, passing through the muscular part of the diaphragm and emerging between the fifth and sixth true ribs on the left side. The wound healed externally [end of initial phase], but he continued to have a stomach disorder like a sort of colic so he could eat

TABLE IV.—CONTENTS OF HERNIAS FOUND AT OPERATION

Left hemithorax—20 cases	
Stomach	13
Greater omentum	12
Transverse colon	11
Spleen	10
Splenic flexure colon	9
Small bowel	7
Ascending colon	2
Sigmoid colon	1
Descending colon	1
Pancreas	1
Right hemithorax—2 cases	
Right lobe of liver	1
Right kidney	1
Ascending colon	1
Cecum	1
Appendix	1
Small bowel	1

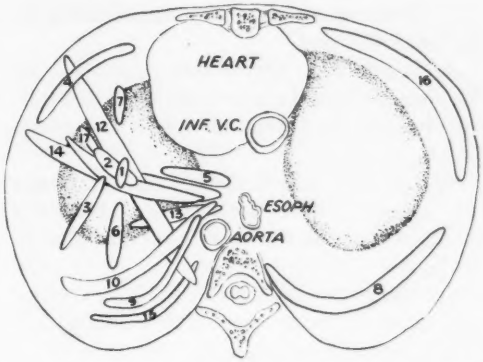


FIG. 6. Site of 17 tears from indirect trauma inflicted upon right and left hemidiaphragm as seen from above.

only sparingly. Eight months later [end of latent phase] he developed severe colic-like pain in the epigastrium . . . he died [end of obstructive phase]. At autopsy . . . in the thorax was found a large part of the colon filled with air; it had entered through a hole only large enough to admit the tip of the little finger, made through the diaphragm by the wound."

If the possibility of injury to the diaphragm after nonpenetrating injuries to the thorax and abdomen is kept in mind, the number of correct diagnoses will increase accordingly. Serial roentgenograms of the chest may show alterations above the normal convexities of the diaphragm to those compatible with traumatic hernia even in the early stages after injury.

Penetrating wounds of the thorax and abdomen must be viewed in light of the remarkable mobility of the diaphragm and also with respect to the position of the patient at the time the injury was sustained. It is only after these considerations that the diaphragm may be visualized in the path of a missile.

The physical examination is of the utmost importance. The clue to a ruptured diaphragm may be observed in the paradoxic motion of the left upper quadrant of the abdomen. Carson and Huelsman, in 1912, and Gibson, in 1929, described asymmetry of the hypochondria. Gibson's astute observation was as follows: "A depression in the epigastrium and beneath the costal margin of the affected side—a condition that was accentuated by inspiration and associated with a deviation of the linea alba to the left." Lui and associates redescribed the sign in 1958.

Adams and Musselman have called attention to the "triad of injury" in patients with rupture of the diaphragm. Damage to the kidney or spleen should bring to mind the possibility of injury to the diaphragm to complete the triad. On the right side, one should view the diaphragm with care while investigating renal and hepatic injuries.

Because of the unpredictable extent of concomitant injuries, a fixed approach to the surgical repair of diaphragmatic trauma in the initial phase is undesirable. The abdominal, thoracic, or thoracoabdominal approach may be used effectively as the situation dictates. In the latent phase, the thoracic approach is superior. However, in the obstructive phase, the thoracic approach with an abdominal extension or separate abdominal incision remains the preferable method.

SUMMARY AND CONCLUSIONS

1. Traumatic diaphragmatic hernia is becoming more common because of the increase in high speed travel.

2. Trauma to the diaphragm may be direct or indirect.

3. Traumatic herniation through the diaphragm may be obscured by concomitant injuries and remain occult for many years.

4. The early physical signs and symptoms are meager before the abdominal viscera have penetrated deeply into the pleural cavity.

5. The progression of this injury can be divided into three phases: (1) initial, (2) latent, and (3) obstructive.

6. The majority of traumatic hernias occur on the left because of the diminished buffering force on the under surface of the left hemidiaphragm.

7. Cyanosis and dyspnea may be indications for surgical intervention to relieve mediastinal compression.

8. Roentgenograms may be misinterpreted as "eventration of the diaphragm," "gastric dilatation," or lesions in the lower lung fields.

9. A dilated stomach in the left pleural cavity may simulate a tension pneumothorax.

10. Fractures of the pelvis and lumbar vertebrae should alert the examiner to the possibility of traumatic diaphragmatic hernia.

11. Diaphragmatic injury should be considered in conjunction with possible trauma to the liver, kidneys, and spleen.

12. Intestinal obstruction may occur with few significant abdominal findings, when the majority of abdominal viscera are in the left hemithorax.

13. The thoracic surgical approach is superior to the abdominal. However, extensions or separate incisions may be necessary to deal with concomitant injuries.

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TOTAL BODY POTASSIUM IN PATIENTS AFTER URETEROILEOSTOMY

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HYPOKALEMIA following ureterosigmoidostomy was first reported by Foster, Drew, and Wiss. Additional cases of hypokalemia even to the point of flaccid paralysis have been published. Stamey presented clinical and pathologic evidence to support the view that the bodily stores of potassium are depleted in many patients after ureterosigmoidostomy even though the serum potassium may be normal. This observation led us (3) to measure the total body potassium in active asymptomatic patients after ureterosigmoidostomy. The potassium stores were found to be significantly decreased below those of a control group of normal individuals.

This article is a report of the total exchangeable body potassium in a group of patients after ureteroileostomy.

MATERIAL AND METHODS

Total exchangeable body potassium (T.E.K.) was measured in 12 adult male patients from the Minneapolis Veterans Administration Hospital. Each had had a ureteroileostomy from 1½ to 60 months prior to the time of this study. All were asymptomatic, in apparent good health, and normally active. In 10 patients ureteroileostomy was performed after cystectomy for neoplasms of the bladder and in 2 for hydronephrosis of a solitary kidney following tuberculous destruction of the opposite kidney and the bladder. None of the patients suffered from acute pyelonephritis postoperatively.

Follow-up investigation with excretory urograms and with retrograde injection of the loop with contrast media has shown either no change or improvement of the upper urinary tract in these patients.

Recent data indicate that T.E.K. of normal persons decreases with age. The 11 male control patients were matched closely for age with the experimental group (Table I).

T.E.K. was measured after the manner of Corsa and Aikawa and their associates. A sterile solution of radioactive potassium, K^{42}, was injected intravenously. The average dose was 250 microcuries, average 400×10^5 counts. A 24 hour urine specimen was collected to determine K^{42} loss. A minimum of 2 counts for 5 minutes was made on each of 2 aliquots of urine of 4 milliliters each to determine their radioactivity. Two 1 hour equilibrium specimens were obtained after 24 hours. A minimum of 2 counts for 5 minutes on each of 4 equilibrium urine aliquots of 4 milliliters each was made for the determination of their radioactivity. Potassium concentration of the urine was determined with the flame photometer. T.E.K. was calculated using the following formula:

$$\text{T.E.K.} = \frac{K^{39}\text{ equilibrium urine } (K^{42}\text{ injected} - K^{42}\text{ excreted})}{K^{42}\text{ equilibrium urine.}}$$

RESULTS

In the 12 patients after ureteroileostomy the average T.E.K. was 38.6 milliequivalents of potassium per kilogram of body weight. The 11 control patients had an average T.E.K. of 38.8 milliequivalents of potassium per kilogram of body weight. These data are summarized in Table I.

Patient 7 had a rather low T.E.K. of 29.5 milliequivalents of potassium per kilogram of body weight. This was unchanged from a

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measurement made 7 months previously. This patient will be discussed later.

Patient 3 was very obese. His T.E.K. was 31.7 milliequivalents of potassium per kilogram of body weight. On the basis of lean body weight his T.E.K. was probably near normal.

DISCUSSION

The average bodily store of potassium is significantly decreased after ureterosigmoidostomy, whereas it is usually normal after ureteroileostomy. Despite the differences between these two methods of urinary diversion there are two things which these patients have in common: a piece of bowel is interposed between the urinary tract and the exterior of the body, and potassium losses can theoretically occur only from the bowel and the kidneys. A review of the possible mechanisms by which potassium could be lost from such a system follows.

MECHANISMS OF POTASSIUM LOSS

Renal cation loss. The most significant clinical electrolyte problem following ureterosigmoidostomy is the development of hyperchloremic acidosis in a high percentage of cases. Most observers agree that hyperchloremic acidosis following ureterosigmoidostomy is a reflection of excessive chloride reabsorption and that the severity of the problem is proportional to renal function. After a ureteroileostomy, patients often manifest a similar hyperchloremia for a short time in the early postoperative period. Permanent hyperchloremic acidosis is unusual in persons with ileac diversion and when seen is usually associated with severe renal damage.

A unique demonstration of absorption of various urinary constituents from the bowel was made by Parsons, Powell, and Pyrah. They performed preliminary colostomy and unilateral ureterosigmoidostomy in preparation for cystectomy; one kidney drained into the bladder and the other into the isolated rectosigmoid. The bladder was removed at a second stage and the other ureter was transplanted to the bowel. They compared the clearance of creatinine, the volume of urine, and the concentration of potassium in collections from the bladder and rectosigmoid and found them approximately equal. The chloride concentration, however, was diminished 60 to 80 per cent in the rectosigmoid, sodium less so, and nonprotein nitrogen about 30 per cent when compared with the urine from the bladder. In 1 case, bladder urine was instilled into an isolated rectosgimoid for 2 hours, and the absorption of these latter constituents without change in potassium concentration was confirmed.

Annis and Alexander placed urine in the isolated rectosigmoid of 2 patients. Chloride decreased 75 and 50 milliequivalents per liter and sodium only 10 and 30 milliequivalents per liter respectively. Volume and potassium changes of the instilled urine were negligible. These clinical experiments furnished data similar to the later findings of Pers in the dog. When he placed urine into the isolated colon of a dog, chloride reabsorption varied from 29.9 to 77.5 per cent with urine of specific gravity greater than 1.019 and from 82.1 to 98.5 per cent with urine of specific gravity less than 1.019. Net reabsorption of sodium was significantly less than of chloride. With hypertonic urine, sodium was even secreted into the lumen in a few instances despite a great amount of chloride reabsorption. Net potassium exchange was negligible in the experiment.

If chloride is absorbed avidly in the bowel, reabsorption of a cation to preserve electroneutrality will occur. From these data, sodium and potassium were not the cations primarily involved. Hydrogen is the only other ion present in suitable amounts. It is also available from titratable acid and ammonium in urine. Pers found that hydrogen ion equivalents[1] were absorbed from a dog's

[1]Pers expressed this relationship with the following formula:

$$H^+ \text{ equivalent} = \frac{\text{Titratable acid} + NH_4^+}{HCO_3^-}$$

Although NH_3 may be formed in the bowel from bacterial action on urea, there is no net gain of hydrogen in the formation of more NH_4^+ since a corresponding decrease in titratable acid occurs and the above ratio remains unchanged. Boyce and Vest had previously surmised that the predominant cation reabsorbed was ammonium.

TABLE I.—DATA ON PATIENTS AFTER URETEROILEOSTOMY

Patient	Wt., kgm.	Age, yrs.	Months with uretero-ileostomy	BUN	Na	K	CO_2	Cl	T.E.K., mEq.	T.E.K., mEq. per kgm.	24 hour K† excretion, mEq.
EXPERIMENTAL GROUP											
1	57.0	67	1.5	14	133	5.6	26.6	96	2128.6	37.3	—
2	56.4	64	23	12	139	4.6	27.4	105	2516.5	44.6	—
3	91.8	63	44	13	139	4.8	29.2	106*	2905.5	31.7	—
4	73.0	42	20	41	139	5.3	19.8	110*	2788.9	38.2	—
5	56.1	69	6	21	141	5.2	23.2	108.5*	2442.0	43.5	—
6	71.3	63	5	16	141	4.0	26.2	103	2716.3	38.1	—
7	64.5	66	9	21	146	4.9	24.0	109	1898.0	29.5	—
	64.5	66	16	19	140	4.4	24	101	1900.3	29.5	61.9
8	54.5	69	2.5	26	140	4.7	21.5	111	2065.6	37.9	—
9	70.0	65	60	62	137	4.7	13.8	118*	2588.6	37.0	85†
10	69.4	64	17	22	135	5.0	21.0	102	2694.4	38.8	77
11	60.0	67	13	22	141	5.5	19.3	109*	2537.2	42.3	80.5
12	61.1	32	6	20	140	4.7	21.0	108*	2716.0	44.5	110
		Av. 60.9								Av. 38.6	
CONTROL GROUP											
11	Av. 59.5 (range 46–70)									Av. 38.8 (range 33.9–44.7)	

*Preoperative loss of one kidney or evident preoperative renal damage.
†Estimated from renal clearance data.

colon in significant amounts. This occurred concomitant with absorption of chloride and in inverse proportion to the amount of sodium absorbed. If sodium reabsorption is decreased, or, as in a few of Pers's experiments, even secreted into the lumen, the amount of hydrogen ion equivalents absorbed with chloride would be greater. Hyperchloremic acidosis occurs clinically when hydrogen and chloride ion load in excess of renal excretory capacity is absorbed.

Excessive hydrogen and chloride loads have definite effects on urinary electrolytes. Clarke and associates fed 3 normal subjects ammonium chloride and found increased chloride excretion accompanied by increased sodium and potassium excretion. Sartorius and co-workers had likewise shown increased potassium and other cation excretion with ammonium chloride ingestion. Similarly hyperchloremic acidosis is probably the mechanism of potassium loss following ureterosigmoidostomy, except that the anion is "ingested" from urine. After ureterosigmoidostomy, the bowel retains urine for up to several hours; urine containing contrast agent placed in the rectum has been demonstrated by Lapides and Stamey to wash the entire large bowel. In these cases urine is presented to a large surface area of intestine with ample time for reabsorption of hydrogen and chloride ions. The greater the hydrogen and chloride ion absorption, the greater the renal cation loss.

Since the bowel is used only as a conduit after ureteroileostomy, urine is in contact with mucosa for a short time. Under such circumstances absorption of hydrogen and chloride is minimized and renal potassium losses are lessened. This fact probably explains the normal T.E.K. in the group of persons reported who have had a ureteroileostomy. Basically the same mechanisms operate in either mode of urinary diversion but reabsorption is by comparison greater after ureterosigmoidostomy than after ureteroileostomy. Only if an excessive length of ileac loop is used or free drainage is impaired would absorption of any magnitude occur. Thus, renal potassium loss is proportional to the load imposed by anion reabsorption from the gut.

Osmotic diuresis. A significant absorption of urea by the colon was demonstrated by Parsons and associates and by Annis and Alexander. In Pers's experiments using a dog's colon, urea absorption varied from 4.1 to 37 per cent with urine of specific gravity greater than 1.019 and 27.5 to 64 per cent with urine of specific gravity less than 1.019. A normal person excretes 15 to 35 grams of urea per day, 6 to 14 grams of urea nitro-

gen. This amount depends mostly on dietary protein intake. If reabsorption of urea nitrogen after ureterosigmoidostomy would average 30 to 40 per cent, one could expect to find at least a mild osmotic (urea) diuresis in these individuals. Mudge and Anslow and their associates have demonstrated significantly increased potassium excretion with a massive urea diuresis in dogs. One might speculate that the milder diuresis seen after ureterosigmoidostomy can result in potassium losses. This theory should be considered until it can be proved that renal conservation of potassium is not inhibited by such a diuresis. At any rate, such a mechanism would play only a negligible part in potassium loss after ureteroileostomy since there is less opportunity for reabsorption of urea than after ureterosigmoidostomy.

Renal damage. As noted before, a normal person challenged with an excess anion load excretes more sodium and potassium. This is much the same situation that occurs after ureteroenterostomy. With renal damage an excess acid load is merely presented to fewer nephrons. One would expect more prolonged potassium losses, since even a normal kidney responds slowly to conserve potassium.

Pyelonephritis is certainly more common in persons after ureterosigmoidostomy than after ureteroileostomy. Clinical episodes of pyelonephritis occurred after ureterosigmoidostomy in all the patients previously studied for T.E.K. (3) but in none of the present series similarly studied after ureteroileostomy. Although pyelonephritis can lead to a specific renal tubular defect with secondary loss of cations, such a "salt losing" defect is rarely reported. According to Franklin and Merrill, only 20 cases have appeared in the literature since 1944. Recently, Owen and Verner have observed 10 patients with flaccid paralysis and hypokalemia. Eight of these patients had definite histories of pyelonephritis; they lost abnormal quantities of potassium in the urine. The defect apparently consists of tubular damage greater than glomerular damage; hence, the glomerular filtrate load is handled inadequately by the tubules. One would have to postulate a similar lesion affecting the tubular function after every ureterosigmoidostomy in order to explain the low body potassium being secondary to pyelonephritis, which seems unlikely.

Hydronephrosis has either improved, not changed, or not occurred after ureteroileostomy in the majority of cases reported in the literature. This is true of the 12 cases in this study. After ureterosigmoidostomy, however, hydronephrosis is a problem both from stenosis of the transplanted ureter and from urinary reflux. Again it seems unlikely that significant losses of potassium could result from uncomplicated hydronephrosis; such losses have not been reported. Excessive cation excretion has followed sudden relief of hydronephrosis.

We believe that pyelonephritis and hydronephrosis exaggerate existing imbalances but are not necessarily causative in the development of hyperchloremic acidosis or potassium losses.

Intestinal potassium losses. One might speculate that potassium secretion into the lumen of bowel containing urine could explain an excessive loss in ureterosigmoidostomy. D'Agostino, Leadbetter, and Schwartz instilled isotonic saline into the isolated colons of dogs and found sodium was reabsorbed in exchange for potassium, milliequivalent for milliequivalent. However, isotonic saline is unlike normal urine; such a speculation ignores the effect of the specific gravity, *p*H, titratable acidity, ammonium, phosphate, sulfate, and urea concentration on net sodium and potassium movements. This fact was borne out in later experiments in which urine instead of saline was placed in the bowel lumen. Parsons and associates and Annis and Alexander found no significant net changes in potassium concentration with urine in the human colon. Pers likewise noted no net change in the amount of potassium in the urine in a dog's colon.

There is one set of circumstances in which enteric secretion of potassium might occur.

Pyrah and associates found net potassium movement into the lumen of a segment of ileum when he instilled a fluid isotonic except for potassium of concentration less than 15.96 milliequivalents per liter of perfusate. One can only speculate whether or not potassium would be secreted into the lumen of either ileum or colon in the presence of urine with a similarly low concentration of potassium. Certainly excess potassium secretion can occur in the bowel since significant losses occur in diarrhea. After ureterosigmoidostomy or ureteroileostomy, dilution of the intestinal contents with subsequent lowering of intraluminal potassium concentration may occur by water diuresis or by the polyuria of urea diuresis or the polyuria of potassium depletion nephropathy. Potassium depletion nephropathy is particularly interesting in this regard. Oliver and associates, using their microdissection technique, found that the collecting ducts and the proximal tubules were damaged. These are not the areas involved with potassium secretion, but when these are damaged the ability to reabsorb water is seriously impaired. Polyuria ensues. After ureterosigmoidostomy a vicious cycle could ensue as the potassium losses caused further polyuria with secondary intestinal secretion of potassium.

Miscellaneous. Factors ordinarily not operating after ureterosigmoidostomy and ureteroileostomy which do increase potassium losses are sodium loads, dehydration, steroid administration, extra administration of ammonium chloride in cardiacs, mercurial diuretics, carbonic-anhydrase inhibitors, and aldosteronism. After ureterosigmoidostomy some patients have received extra sodium to combat acidosis. Since sodium loads can increase potassium losses it would probably be well not to give sodium alone.

URETEROILEOSTOMY WITH DECREASED TOTAL EXCHANGEABLE BODY POTASSIUM

Patient 7 had a decreased T.E.K. with normal serum potassium. He is healthy except for occasional epigastric distress. There is no ready explanation for his potassium deficit unless he had an excessive length of ileal loop with increased anion absorption and secondary renal cation losses. Even with a low T.E.K. he excreted 61.9 milliequivalents of potassium per 24 hours in 1,820 milliliters of urine.

To avoid the possibility of increased potassium losses after ureteroileostomy it would seem desirable to make the loop as short as possible.

POSTOPERATIVE MANAGEMENT WITH URINARY DIVERSION

Ureteroileostomy. Since no abnormality of total exchangeable body potassium is present in most patients after ureteroileostomy, no routine treatment seems needed. Sometimes the use of a long loop of ileum may be necessary. If hyperchloremia occurs it would be evident that an excessive reabsorption of anion is occurring. It would seem desirable in such a case to give the patient dietary potassium supplements.

Ureterosigmoidostomy. On the other hand, total exchangeable body potassium is decreased in ureterosigmoidostomy patients and potassium supplements are indicated. Potassium citrate or lactate would seem best in order to minimize excess anion loads. Potassium can be given to anyone with hypokalemia and hyperchloremic acidosis. When there is renal failure, potassium should be withheld until examination of serum electrolytes is completed. Patients with decreased renal function handle potassium very slowly, and there is always danger of hyperkalemia occurring when potassium loads are given. The real problem arises in essentially normal-appearing patients with normal serum potassium. Except with notable potassium depletion, serum potassium does not reflect the total body potassium but rather the serum *p*H. Empiric administration of potassium seems justified in view of the potassium deficiency demonstrated in our ureterosigmoidostomy patients (3).

Stamey has commented on the necessity of giving potassium to patients after ureterosigmoidostomy when they are acutely ill

with progressive hyperchloremic acidosis. Administration of sodium chloride solutions may only hasten their demise since sodium is a "toxic ion" in the presence of potassium depletion.

SUMMARY

Total body potassium was measured in 12 otherwise healthy patients after ureteroileostomy. The average total body potassium was the same as that found in a control group of the same age and sex.

Intestinal absorption of hydrogen and chloride ions may result in excessive renal potassium wasting. The process may be accentuated the longer urine is in contact with the intestinal mucosa, for instance, in patients who have had a ureterosigmoidostomy or those with excessively long or poorly draining ileal loops. Osmotic diuresis, renal damage, and intestinal secretion of potassium probably contribute to the lack of potassium conservation by these patients.

The management of potassium loss in urinary diversion is discussed.

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THE TREATMENT OF IRRADIATION SICKNESS IN THE DOG WITH AUTOLOGOUS AND HOMOLOGOUS BONE MARROW

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EXPERIMENTS in mice, rabbits, rats, and guinea pigs have demonstrated that intravenous administration of autologous or homologous bone marrow homogenates protects animals so treated from death following exposure to irradiation which would be lethal in untreated animals. Studies in the dog are quite limited as compared to those in smaller animals, but the reported results are, in general, less successful. An early study by Rekers, Coulter, and Warren demonstrated that intravenous administration of autologous marrow reduced the mortality rate in dogs subjected to 350 roentgens of total body irradiation from 67 per cent to 43 per cent. Sullivan and associates reported that 7 of 8 animals treated with autologous marrow which had received 400 roentgens of total body irradiation survived as compared to 1 of 6 animals in an untreated group; however, autologous marrow failed to prevent death following exposure to 450, 550, and 600 roentgens. They concluded that this modality of therapy was useful only at marginal doses of irradiation. Alpen and Baum have recently obtained a 64 per cent survival rate following exposure to 470 rads. Still better results with autologous marrow were obtained by Kelly, Lamb, and Condie who noted that the dosage of cells was important. In animals exposed to 480 roentgens without marrow administration the fatality rate was 100 per cent. It was also 100 per cent in animals treated with doses of bone marrow less than 1.5 billion cells. In animals treated with doses of more than 2 billion cells, however, the survival rate was 10 of 13 animals.

The experience with homologous marrow has been discouraging. In 1957, Allen and associates noted that no mongrel dog had survived lethal doses of total body irradiation by treatment with homologous marrow. The only dogs that have survived after irradiation exposure treated with homologous marrow are reported by Thomas and associates who have obtained a few survivals in beagle hounds.

The present experiments were performed in an attempt to gain further experience with transplantation of autologous and homologous marrow in dogs.

TRANSPLANTATION OF AUTOLOGOUS MARROW

Materials and methods. Mongrel dogs were utilized in this experiment. Each animal was observed during a quarantine period of 2 weeks, and only healthy animals were selected for this study. Treatment for intestinal parasites was performed if infestation was present. Preirradiation studies included white cell, differential, red cell, and platelet counts, hemoglobin concentrations, and hematocrit determinations. Irradiation was administered in calculated surface doses of 400, 500, 600, 700, 850, and 1,000 roentgens utilizing the 2,000 kilovolt Van de Graaff machine at 135 to 200

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TABLE I.—EFFECT OF AUTOLOGOUS MARROW ON WHITE CELL COUNTS OF DOGS SURVIVING TOTAL BODY IRRADIATION

Dog No.	*X-ray dose, roentgens*	*Dose of bone marrow, bil. cells*	*Lowest white cell count, cells/cu. mm.*	*Lowest count*	*Recovery*
				Time in weeks	
780	700	.6	—	—	6
827	700	2.4	150	2.0	6
842	700	1.7	500	1.3	5
846	700	1.2	450	1.3	5
851	700	1.6	600	1.1	5.5
856	700	1.6	450	1.8	8
879	700	1.7	550	2.0	5
914	850	1.3	250	2.0	4
945	850	3.9	950	2.0	5

amperes through an 8 millimeter lead filter. Irradiation was administered to anesthetized animals as a single dose through 2 ports, one-half of the dose being administered on the right and one-half on the left side at a distance of 215 to 217 centimeters. The treatment time was approximately 1 hour in most animals. In the postoperative period, 500 milligrams of achromycin were administered daily for the first 2 weeks; no other special supportive therapy was given. The pretreatment hematologic studies were repeated on the first, third, fifth, seventh, fourteenth, twenty-first, and twenty-eighth days. These studies were repeated at monthly intervals in those animals surviving longer.

Thirty animals were subjected to the regimen described, but without marrow administration, in order to establish the mortality rates at varying doses of irradiation. Of these, 4 dogs received 400 roentgens, 4 dogs received 500 roentgens, 4 dogs received 600 roentgens, and 18 received 700 roentgens of total body irradiation.

Twenty-eight animals were treated with bone marrow after irradiation exposure. In 2 of these, marrow was collected by irrigation and aspiration after drilling through the cortex at each end of one femur. This method gave a low yield of cells, approximately .5 billion; therefore, in the remaining animals marrow was aspirated from the iliac crest. During aspiration the syringe was wet with heparin to prevent clotting. With this technique 1 to 4 billion cells could be harvested in 15 to 20 minutes.

In each instance the animal was anesthetized and marrow was aspirated. The calculated dose of irradiation was then administered. While irradiation was being administered, the marrow was diluted with an equal volume of Earle's solution and stored in a refrigerator. The marrow was injected intravenously as soon as irradiation was completed. Fourteen animals were treated with doses of bone marrow ranging from .4 to 2.8 billion cells after the administration of 700 roentgens of total body irradiation. Eight animals were treated with .8 to 3.9 billion cells after administration of 850 roentgens, and 6 animals were treated with 1.0 to 2.8 billion cells after administration of 1,000 roentgens of total body irradiation.

Results. The irradiated animals appeared quite healthy immediately after reaction from anesthesia and for several days maintained a good appetite and were normally active. Most animals became listless and anorexic on the ninth or tenth day following irradiation and those that failed to survive died within 48 to 72 hours after the first sign of illness. Those animals that survived rapidly regained their appetite and returned to a clinically normal status.

Two of the 4 control dogs exposed to 400 roentgens survived, while only 1 of the 4 dogs exposed to 500 roentgens survived. None of the 4 control dogs exposed to 600 roentgens or of the 18 exposed to 700 roentgens survived. In those dogs that died, the length of life following irradiation varied from 5 to 21 days with a mean of 11 days. In general, the animals treated with lower doses survived longer than those treated at higher doses, for the longest survival in untreated animals receiving 700 roentgens was 16 days.

Seven of the animals treated with bone marrow after administration of 700 roentgens of total body irradiation survived for more than a month, and the hematologic alterations returned to normal. One of these animals expired of undetermined causes 42 days after irradiation whereas the remaining 6 are alive and well for periods exceeding

15 months. Only 2 of the 8 dogs treated after exposure to 850 roentgens survived. Both of these are alive for periods of 6 and 7 months respectively after irradiation. None of 6 dogs survived exposure to 1,000 roentgens. Each of the latter animals developed a bloody diarrhea, and the longest survivor lived 13 days, this being the only animal that survived more than 8 days. Necropsy revealed severe hemorrhagic ulceration of the gastrointestinal tract, and it is believed that these animals died from gastrointestinal complications rather than from marrow depression.

Studies of the changes in the peripheral blood cells demonstrated a fall in the total white count. The lowest white cell counts in dogs exposed to 400 roentgens were observed 3 weeks postirradiation, after which time recovery occurred in the 2 dogs that survived. After administration of 500 roentgens, there was a more rapid fall in the white cell counts, the lowest counts being observed at 2 weeks. With higher doses of irradiation, the lowest white cell counts were observed at periods varying from 8 days to 2 weeks (Fig. 1). The return to normal pretreatment levels required from 4 to 6 weeks from the time of irradiation, that is, 2 to 4 weeks after the low point observed (Table I). All surviving animals demonstrated a return to normal pretreatment levels of blood counts except 1. This animal, exposed to 850 roentgens, has demonstrated a persistent leukopenia, the total count varying from 3,000 to 5,000 white cells per cubic millimeter, as compared with a preirradiation count of 8,000 cells per cubic millimeter.

A similar depression with recovery was noted in the red cell series and in the platelet count.

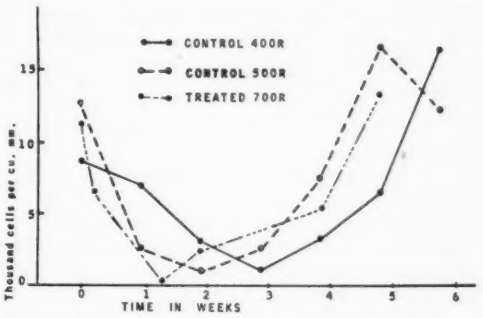

FIG. 1. The effect of total body irradiation on the white cell counts of control and treated dogs.

TRANSPLANTATION OF HOMOLOGOUS MARROW

Materials and methods. Two different therapy units were utilized for irradiation of dogs in the study of marrow homografts. One was the Van de Graaff machine, using the technique described previously. The second machine was a 220 kilovolt therapy unit. Using the latter machine, irradiation was administered through 4 to 6 ports—2 or 3 on each side—with the total dose being administered in 20 to 45 minutes at a distance of 50 centimeters through a one-half value layer 2 millimeter copper plus 1 aluminum filter. Four control dogs received 350 roentgens, 7 received 400 roentgens, 4 received 450 roentgens, 1 received 525 roentgens, 5 received 600 roentgens, and 3 received 750 roentgens.

Homologous marrow was obtained for dogs irradiated with the 220 kilovolt machine by sacrificing a donor animal and harvesting all possible marrow from the long bones and pelvis. The number of cells obtained varied from .8 to 6.5×10^9 cells in adult dogs. A marrow homogenate was prepared, in some instances by passing the marrow through screens of varying sizes, at other times by using an electric homogenizer. The cells were then suspended in varying solutions, including normal saline, Ringer's lactate, and Earle's solution with and without the addition of serum from the donor dog. In a few instances, pure serum of the donor dog was used as the suspending fluid for the cells.

Several different techniques were used in attempts to modify the rejection mechanism. Each of these will be described in the following.

I. Animals irradiated with the 220 kilovolt machine.

1. Each of the following animals received 400

roentgens in a single dose through 4 to 6 ports, this dose having been established as the lethal dose.

a. Six dogs were treated by marrow administered intravenously immediately upon completion of the irradiation dosage.

b. Four dogs received marrow intravenously 3 days following completion of irradiation.

c. Splenectomy was performed 10 days prior to irradiation administration in 4 dogs. Bone marrow was then injected immediately after completion of the irradiation. Starting on the day of treatment 25 milligrams of cortisone were given parenterally and daily for the duration of the experiment.

d. In 2 dogs 20 units of adrenocorticotropic hormone (ACTH) was administered daily for 10 days prior to the time of irradiation. On the day of irradiation, the donor dog was exsanguinated, the blood being collected in a sterile container for transfusion. The donor dog was then sacrificed and marrow collected as described before. Immediately after irradiation, an exchange transfusion was performed, substituting the donor dog's blood for the host's. After the exchange transfusion had been completed the donor marrow was injected intravenously. ACTH administration was continued in the postoperative period.

e. Four dogs received marrow obtained from 1 puppy 3 months old rather than from an adult dog. The technique for harvesting marrow was the same as that described in harvesting marrow from the adult dogs. The marrow was administered intravenously immediately after completion of irradiation.

f. Twelve puppies, each known to be 3 months of age, were purchased. These constituted 6 sets of litter mates, 1 male and 1 female from each litter. One set was full-blooded boxer, one set full-blooded cocker, while 4 sets were mongrels. Ten days to 2 weeks prior to irradiation, splenectomy was performed, and administration of ACTH, 20 units daily, was instituted. Sex cell counts were made in all animals. One of the puppies was then subjected to total body irradiation and the litter mate was used for the donor animal. The doses of marrow in these dogs were 3×10^8, 8×10^8, 3.5×10^9, 4.6×10^9, 5.3×10^9, and 6.5×10^9 cells respectively. ACTH administration was continued in the postirradiation period.

g. Three adult dogs were treated with fetal marrow, obtained by harvesting marrow from bones of fetuses removed from pregnant females by cesarean section. In order to obtain the maximum dose possible, bones from all fetuses in a litter were combined to make 1 dose. Even with this pooling of marrow from 4 or 5 fetuses, however, the yield was low, approximately 3×10^8 cells. The fetal marrow was administered immediately after completion of irradiation.

2. Eight hundred roentgens were administered in divided doses to 7 dogs. Four hundred roentgens were administered on the first day. On the second day splenectomy was performed, and a second dose of 400 roentgens was administered. Marrow was injected intravenously immediately after completion of irradiation exposure. The animals were given cortisone parenterally on the day of irradiation and daily throughout the rest of the experiment in doses of 25 milligrams.

II. Animals irradiated with the Van de Graaff machine:

1. Four animals, each receiving a single exposure to 850 roentgens, were treated with adult homologous bone marrow obtained from a donor dog by aspiration of the iliac crest as described previously in the section on autologous marrow. Two of these animals received 1 dose of marrow immediately after irradiation. One animal received 2 doses of marrow, one administered immediately after the irradiation, the second administered 3 days later. Three doses of marrow were administered in the fourth animal, one on the day of irradiation, one 3 days later, and the third 3 days following the second dose. The total dose of marrow in this dog was 5×10^9 cells.

Results. The results in control dogs receiving irradiation from the Van de Graaff machine are described in the section on autologous marrow.

One of the control dogs given 350 roentgens of total body irradiation with the 220 kilovolt machine survived, a survival rate of 25 per cent. No animal receiving a higher dose survived. The animals exposed to 400 roentgens survived from 8 to 12 days, with an average survival of 9 days. Animals exposed to greater amounts died in shorter periods, no animal living beyond 10 days. The average survival time for animals given 600 roentgens was only 5 days and the 3 animals given 750 roentgens lived only 2 days after irradiation.

None of the animals treated with homologous marrow survived for a period significantly longer than the controls, the longest survival being 13 days. The longest survival in the group of litter mate puppies was 10 days (Table II). Except for a few animals expiring on the day of irradiation, in which improper preparation of the marrow homogenate could not be excluded as a factor in the death of the animal, the clinical course of the animals treated with homologous marrow did not differ significantly from the course of the untreated controls.

DISCUSSION

This experiment demonstrated that autologous marrow offers some protection against the lethal effect of irradiation. Though protection is not 100 per cent, some protection was observed at higher levels of irradiation than recorded by other observers. The dogs used in this study of autologous marrow were kept in the usual kennels and given no special protection except for antibiotic administration. It is likely that pure, bred animals in a protected environment would have a higher survival rate.

It is also likely that a significant increase in the average dose of marrow cells administered might result in a higher survival rate than was observed here. We have demonstrated, however, that protection is possible at a lower dosage range than reported by Kelly and associates who noted that doses less than 2 billion cells were relatively ineffective. The harvesting of a large dose of autologous marrow has been one of the difficulties limiting this type of experiment, for doses of marrow exceeding 2 billion cells could not be obtained without subjecting the animal to undesirable trauma by previous techniques. It has now been demonstrated that multiple aspirations from the iliac crests alone, for a period of several days, may allow harvest of 6 to 8 billion cells, and others have demonstrated that aspiration from multiple sites including the ribs, vertebrae, sternum, and iliac crest will allow harvesting of even greater numbers of cells. It is worth noting that aspiration of cells has allowed a greater number of cells to be obtained from the pelvis than often could be obtained from multiple bones after sacrifice of the dog. This method is also of significance in that it is less time-consuming than harvesting of marrow in the sacrificed dogs and because it allows survival of a donor dog when homologous marrow is utilized; thus, repeated doses can be administered if desired.

Other investigators have utilized different methods of administering marrow. Rekers and associates reported its administration

TABLE II.—HOMOLOGOUS MARROW TRANSPLANTS FOLLOWING IRRADIATION EXPOSURE WITH THE 220 KILOVOLT THERAPY MACHINE

No. dogs	10	4	2	4	6	3	7
400 roentgens single dose	+	+	+	+	+	+	
800 roentgens divided dose							+
Adult marrow	+	+	+				+
Puppy marrow				+			
Litter mate puppy marrow					+		
Fetal marrow						+	
ACTH			+		+		
Cortisone		+					+
Splenectomy		+			+		+
Exchange transfusion			+				
Survivals	0	0	0	0	0	0	0

intra-arterially, into the spleen, into the liver, and directly into the marrow cavity, as well as transplantation of entire pieces of bone. Although there are theoretic reasons why these techniques might be preferable to the intravenous administration, the utilization of them has not improved the results obtained. In fact, it would appear that the best results have been obtained by intravenous administration.

Perhaps the greatest handicap in correlating results of irradiation experimentation is the lack of a uniform understanding of the concept of dose. There is some general appreciation that the biologic effectiveness of irradiation varies with the quality of irradiation; however, the importance of this cannot be confidently assessed until the other variables in reporting dosage have been described and some conventions adopted. Although it is customary to report irradiation exposure as a single value expressed in roentgens it is not implied that this amount of irradiation is delivered uniformly throughout the animal. The variation in exposure to different organs becomes increasingly important as the size of the animal increases. The uniformity of exposure will depend partly upon the quality of irradiation; for high energy irradiation, the uniformity will be improved by greater penetration; for

lower energy, greater absorption in superficial tissues will diminish the amount delivered to a depth. An exposure from a single source of irradiation, from one direction, will give less uniform distribution than 2 or more sources from different directions or some type of rotation tending to approach a 4π distribution. Increasing the source-object distances utilizes the inverse square law to increase the uniformity although decreasing the intensity. Thus, uniformity of dosage can be improved by the use of high energy levels and by increasingly complicated manipulations of the geometry of "source of irradiation" and "object irradiated."

The importance of time-dose relationship is well appreciated but only within broad limits. Observing the considerations of geometry just discussed and allowing that a single value could have some meaning, we are aware that "x" roentgens in 1 exposure would have a completely different quantitative effect from "x" roentgens in 2 exposures given a week apart. We would also anticipate some difference in the effect of dosages administered in 2 exposures a week apart from the same dosage as a continuous exposure during a period of 1 week. We are less able to say what difference might exist if the dose were delivered in 1 minute, as compared to 1 hour or 1 day, and it would be difficult to say whether such differences would be quantitative (compensable by adjusting the dose), or qualitative, or both.

This declaration of uncertainty is to indicate that conclusions as to biologic effects of irradiation at present remain tentative, and currently the only solution to reconciliation of the results obtained by different investigators is to express awareness of the importance of these variables and to offer an informative description of the conditions under which irradiation was carried out.

Although it cannot be proved unequivocally, there seems little question that autologous marrow transplants do survive in the dog and protect animals from irradiation effect. Since autologous grafts of other tissue and organs are possible, there is no reason to doubt that autologous marrow transplants should also be successful in the human. Thus, the policy of banking autologous marrow for administration to patients who are to be treated with large doses of total body irradiation seems well founded. In the case of accidental exposure to lethal doses of total body irradiation, the use of autologous banked marrow is attractive. The fact that there have been no survivals of patients treated with known lethal doses of irradiation followed by homologous marrow administration in which it can be demonstrated that the homologous marrow persisted as a permanent graft parallels the experience in the dog. Whether or not homologous marrow in the human may be temporarily beneficial allowing survival during a period when recovery of the patient's own marrow may occur is not known. In fact, the entire subject of marrow regeneration is still not well documented. Webb and associates, for example, recently reported that regeneration was possible after exposure of bone to doses of irradiation much greater than those commonly employed in total body irradiation experiments. Others, however, believe that Webb's studies demonstrate repopulation of bone marrow rather than survival of bone marrow. Thus, this problem is not solved. There are other experiments, however, to suggest that animals dying from total body irradiation at what is usually considered the lethal dose may die from factors other than simple marrow depression, for survival of dogs receiving 900 roentgens and 1,300 roentgens has been reported when the animals were simply treated with antibiotics, meticulous kennel care, and the use of intravenous fluids and blood. Here again, however, the factor of dosage calculation is extremely important. In our own kennels, we have been unable to prolong the life of animals at these doses despite these measures. We have not attempted to prolong life in the animals that were treated at doses of 400 roentgens and 600 roentgens.

The parallel between the experience in transplantation in the dog and that in the human, to date, suggests that this animal may be particularly valuable in further study of the problem; for if techniques can be developed which allow successful homologous transplantation in the dog, application of similar techniques to humans would certainly be justified.

SUMMARY

One hundred and twenty-two dogs have been exposed to total body irradiation in amounts varying from 350 to 1,000 roentgens. Single and divided doses were used. Fifty-four of these animals were untreated to determine the lethal dosage range. Twenty-eight were treated with autologous marrow and 40 with homologous marrow utilizing a variety of techniques in attempts to modify the homograft rejection mechanism. Fifty per cent of the animals treated with autologous marrow survived exposure to 700 roentgens of total body irradiation, a lethal exposure in untreated animals, while the survival following exposure to 850 roentgens was 25 per cent. No animal survived exposure to 1,000 roentgens irrespective of marrow transplantation. Homologous transplantation of marrow failed to protect any animal against the effects of irradiation irrespective of techniques employed.

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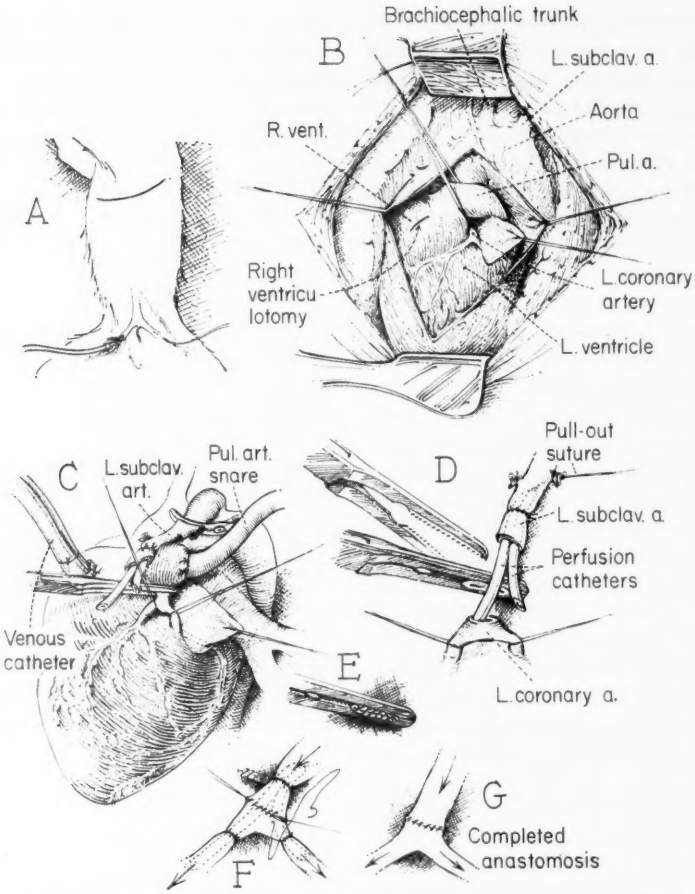

FIG. 1. A, Position of dog for thoracotomy on the left side through fourth intercostal space. B, Operative field. Pericardium opened widely but right pleural cavity not entered. Retraction of main pulmonary artery and left auricle provides good access to left main coronary artery. C, Preparations are completed for start of perfusion and division of the left coronary artery. Left subclavian artery has been divided and turned down with the 2 perfusion catheters in place. Venous drainage catheter in right ventricle and pulmonary artery snare ready. Coronary artery is clamped at aortic root and the left coronary artery is cut flush on clamp. D, The coronary perfusion catheters are inserted into the anterior descending and posterior circumflex artery. Staggering the length of the catheters facilitates cannulation. Pull-out sutures for the catheters are in place and brought out through one of the divided branches of the left subclavian artery. Another vascular clamp is applied beneath the initial clamp on the coronary root to gain a cuff of vessel for closure. E, Aortic end of coronary artery is sutured with running No. 5-0 arterial silk over the clamp. F, Subclavian-coronary anastomosis is performed over perfusion catheters with running No. 6-0 arterial silk. Access to the posterior suture line is greatly facilitated by traction on the perfusion catheters. G, Completed subclavian-coronary anastomosis with perfusion catheters removed via one of the branch stumps using pull-out suture. Coronary flow is not interrupted for this.

Distal Relocation of the Origin of the Left Coronary Artery by Subclavian-Left Coronary Anastomosis.—Richard T. Mamiya, Theodore Cooper, Vallee L. Willman, J. Gerard Mudd, and C. Rollins Hanlon.

DISTAL RELOCATION OF THE ORIGIN OF THE LEFT CORONARY ARTERY BY SUBCLAVIAN-LEFT CORONARY ANASTOMOSIS

RICHARD T. MAMIYA, M.D., THEODORE COOPER, M.D., Ph.D., VALLEE L. WILLMAN, M.D., J. GERARD MUDD, M.D., and C. ROLLINS HANLON, M.D., F.A.C.S., St. Louis, Missouri

ORIGIN OF THE CORONARY ARTERIES in the sinuses of Valsalva and the shortness of the left coronary artery prior to branching have posed many problems in the study and treatment of diseases of the coronary arteries and aortic valve. Studies of coronary blood flow could be facilitated if the coronary ostium were more accessible and if the vessel could be elongated prior to branching. With such a preparation, studies of coronary blood flow and myocardial metabolism could be undertaken in the intact animal in chronic experiments. Experimental replacement of the aortic valve with a prosthesis would be easier if the coronary ostia were at a more favorable location.

With these possibilities in mind, an experimental preparation was created in which the divided left subclavian artery was anastomosed end-to-end to the entire left coronary artery of the dog, thus extending the length of the left coronary artery and transferring its ostium to the aortic arch. This is accomplished by using extracorporeal circulatory support and continuous perfusion of the heart.

METHOD

Mongrel dogs, weighing 16 to 25 kilograms, are digitalized preoperatively with 0.03 milligram of digitoxin per kilogram as a prophylactic supportive measure. Dogs are anesthetized with pentothal sodium and succinylcholine and ventilated with 100 per cent oxygen. Lead II of the electrocardiogram is monitored. One femoral artery is cannulated for pressure monitoring and connected to a pressure transducer. The other femoral artery is cannulated with a No. 18 catheter for the arterial perfusion. A femoral vein is cannulated for measurement of venous pressure and infusion of fluid.

A thoracotomy is performed on the left side, and the pleural cavity is entered through the fourth intercostal space (Fig. 1A). The pericardium is widely opened longitudinally anterior to the phrenic nerve, care being taken not to enter the right pleural cavity. The main pulmonary artery is encircled by a tape for subsequent occlusion and complete venous diversion during cardiopulmonary bypass.

Retraction of the left atrial appendage by a suture, together with retraction of the pulmonary artery, affords adequate exposure of the origin of the main coronary artery (Fig. 1B). The fatty tissue is dissected away from the coronary artery and aortic root. The main left coronary artery, together with its anterior, posterior, and septal branches, is isolated and encircled by ligatures.

The left subclavian artery is freed of all its branches up to the apex of the thorax and divided there. This is turned down for an end-to-end anastomosis to the main left coronary artery. Two polyethylene catheters,

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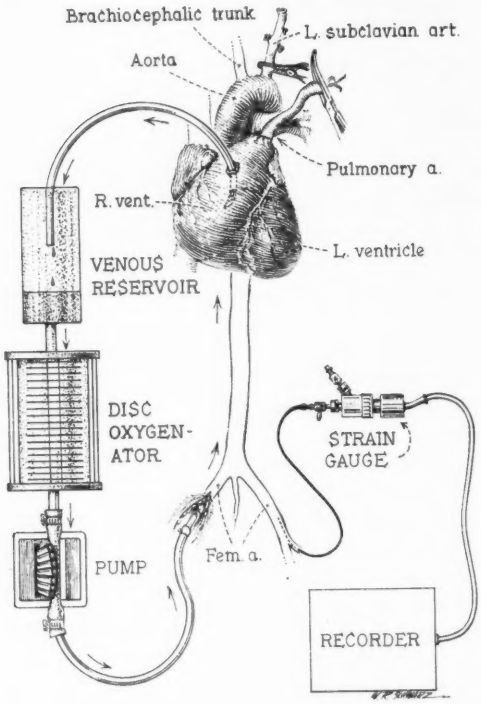


FIG. 2.

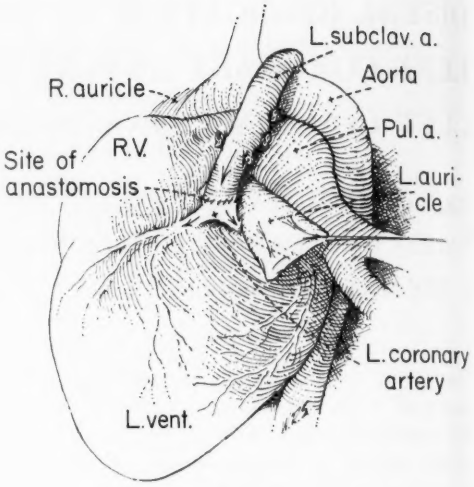


FIG. 3.

FIG. 2. Extracorporeal perfusion system used for subclavian-coronary transfer. Venous drainage from right ventricle through Kay-Cross disc oxygenator by gravity and pumped to femoral artery by sigmamotor pump. Pulmonary artery is snared for complete venous diversion. Strain gauge attached to femoral artery for monitoring arterial pressure.

FIG. 3. Completed procedure with all catheters removed. Right ventriculotomy is closed with running No. 5-0 silk.

corresponding in size to the anterior and posterior coronary arteries, are placed in the distal end of the subclavian vessel to serve as an internal stent for perfusion while the anastomosis is performed (Fig. 1C). A pull-out suture is placed on the proximal end of each of these catheters and brought out through one of the divided branches of the subclavian artery (Fig. 1D). This procedure facilitates removal of the catheters with minimal trauma and without interruption of flow.

After the intravenous administration of 1.5 milligrams of heparin per kilogram, a 3/8 inch tygon tube is inserted into the outflow tract of the right ventricle and allowed to drain into a venous reservoir. This reservoir is connected to a Kay-Cross disc oxygenator by gravity and pumped to the femoral artery by a sigmamotor pump (Fig. 2). The main pulmonary artery is occluded to divert the total output of the right side of the heart into the venous reservoir.

With satisfactory perfusion established and blood pressure maintained at 100 millimeters of mercury, the left coronary trunk is treated in one of three ways depending on its anatomic variation. The objective is to preserve a common coronary trunk so as to require only a single suture line in making the anastomosis. If the common trunk is long enough, the base is tied with a ligature and the vessel divided. If the trunk is shorter the base is clamped with a vascular clamp and the vessel cut flush on the clamp (Fig. 1C). For closure of the aortic end, another clamp is applied beneath the initial clamp and the cuff is oversewn (Fig. 1D,E). If the trunk is very short, the heart is electrically fibrillated, the ascending aorta is cross clamped, and the coronary is cut in such a manner as to preserve some com-

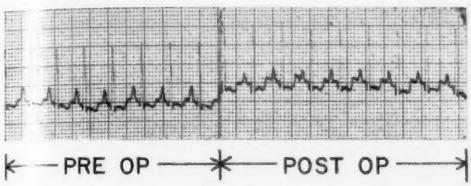


FIG. 4.

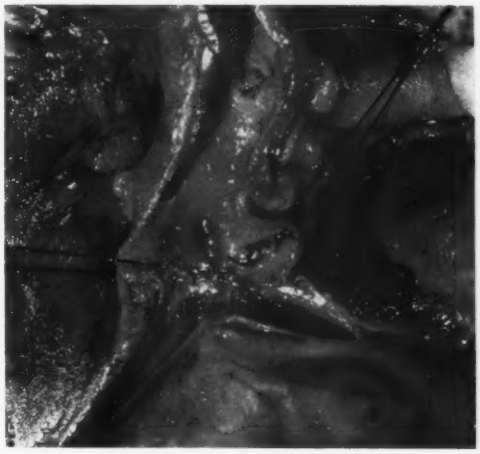
FIG. 4. Lead II of electrocardiogram before and after coronary transfer showing minimal myocardial alteration following the procedure.

FIG. 5. A, Subclavian-coronary artery anastomosis in dog which died 1 week postoperatively from pneumonia. Suture line is clean and the ostium of the septal branch arising from the anterior descending branch is well preserved. B, Closure of left coronary artery ostium in same dog showing no thrombus formation or distortion of valve.

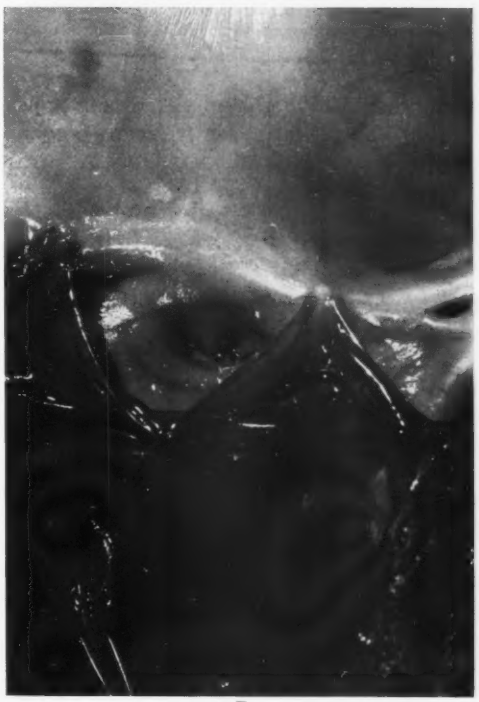
mon vessel, even to the point of taking a button of aortic wall. The aortic defect is then closed by suture under direct vision with care taken not to incorporate the aortic valve in the suture line.

The 2 perfusion catheters in the subclavian artery are then inserted into the anterior and posterior coronary arteries through the main trunk (Fig. 1D). This procedure is facilitated by making one catheter shorter than the other. Ligatures are tied about both vessels, and the occluding clamp on the subclavian artery is removed to start the coronary perfusion. The time for interruption of left coronary flow averages about 2 minutes. The anastomosis is performed over the catheters by using No. 6-0 arterial silk as a continuous suture (Fig. 1F). After anastomosis, the retaining ligatures around the catheters are removed and the catheters are extracted by means of the previously placed pull-out sutures through one of the divided subclavian branches (Fig. 1G). This does not require interruption of flow. Electrical defibrillation is performed if necessary.

Extracorporeal perfusion is discontinued and the right ventriculotomy is closed with No. 5-0 silk after removing the drainage catheter (Fig. 3). Perfusion time averages about 30 minutes. The anticoagulant effect of heparin is reversed with 1.5 milligrams of polybrene per kilogram. The



A



B

FIG. 5.

pericardium is partially closed and the chest is closed around 2 large thoracostomy tubes connected to water-seal drainage. These tubes are left in place until the lungs have completely expanded and there is no

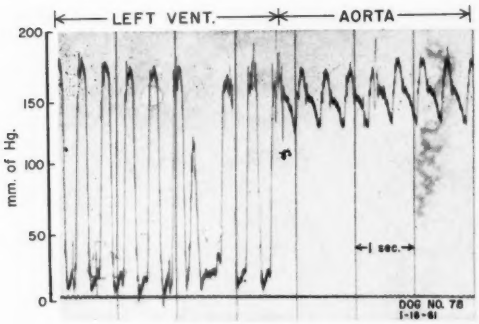


FIG. 6.

FIG. 6. Postoperative retrograde left ventricular catheterization shows normal hemodynamics. Pull-back tracings show no gradient across the aortic valve.

FIG. 7. A, Cineangiogram of aortic root showing good preservation of valve function and annulus with no aortic regurgitation. B, Cineangiogram of subclavian-coronary artery showing well functioning trunk and anastomosis.

evidence of bleeding. Digitalis is maintained for 3 to 4 days, and achromycin and penicillin for 7 days. No anticoagulants are used after operation.

RESULTS

The operation has been attempted 15 times with 10 successes. Five procedures were not completed because of technical errors in the operation or the perfusion. Of 10 dogs surviving operation, 4 are living from 1 to 6 months. Three died on the first day after operation from intrapleural bleeding in 2 instances and aspiration of vomitus in the third. Three other dogs died during the first week from pulmonary infection.

In the long term survivors, studies were made of hemodynamic or myocardial alterations produced by the procedure. Electrocardiograms early in the postoperative period show ST segment changes, but this is transient and patterns essentially similar to control tracings return within 1 week (Fig. 4). No gross or microscopic infarcts are found in the area supplied by the left coronary artery.

Postoperative catheterization studies reveal normal dynamics with no distortion of the aortic valve or annulus. Retrograde

A

B

FIG. 7.

catheterization of the left ventricle with pull-back tracings into the aorta reveals normal pressure relationships (Fig. 6). Cineangiocardiograms of the aortic root show no evidence of aortic regurgitation (Fig. 7A). At autopsy, the competence of the aortic valve is preserved, and the coronary ostium is closed without distortion or thrombus formation (Fig. 5B). It has been regularly possible to enter the left

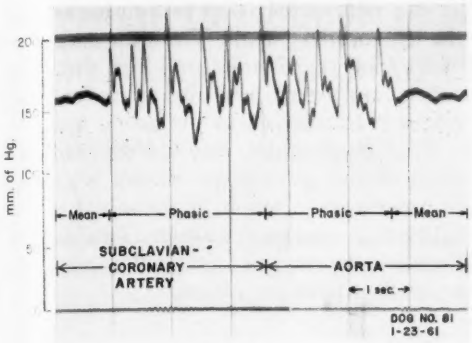


FIG. 8.

FIG. 8. Postoperative pull-back tracings following catheterization of the subclavian coronary vessel show no pressure gradient from this vessel into the aorta. There is no serious interference with flow by turning down the subclavian artery.

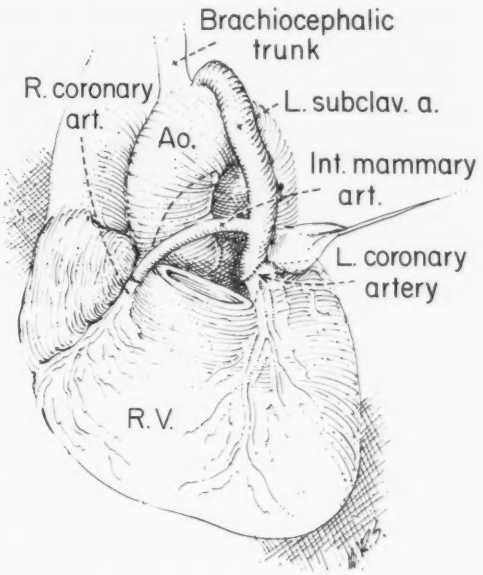


FIG. 9.

FIG. 9. Complete transfer of both right and left coronary arteries into a single left subclavian artery. A longer length of internal mammary artery is preserved than in the previously described subclavian-left coronary transfer. The internal mammary artery is anastomosed end-to-end to the divided right coronary artery. Thus, all the myocardial blood supply originates from the left subclavian artery.

coronary artery by retrograde catheterization through the femoral artery. Pressure tracings show no gradient between this vessel and the aorta (Fig. 8). Cineangiograms with direct injection of this vessel show a normal distal left coronary arterial pattern (Fig. 7B). Exercise is well tolerated save for limping associated with impairment of blood supply to the left upper extremity.

COMMENTS

Despite relatively small and thin-walled vessels, this direct suture anastomosis has proved to be technically feasible. Multiple studies for long periods are not yet available, but in the maximum observation period of 6 months there is no apparent tendency to anastomotic occlusion. Anticoagulants after operation seem unnecessary. An unhurried, accurate anastomosis is facilitated by the perfusion catheters which provide a dry field and adequate myocardial circulation during the time of anastomosis.

The extracorporeal perfusion system with venous drainage from the right ventricle has been highly satisfactory for this procedure. With a large tube, venous drainage is always adequate, and no difficulty has been encountered with closure of the ventriculotomy. In the event of ventricular fibrillation, the heart need not be decompressed for fairly long intervals with this system.

Myocardial damage is minimized by continuous perfusion of the heart while the anastomosis is being performed. During the brief period of interruption of left coronary flow, there is moderate depression of myocardial activity, but as soon as the perfusion is instituted, there is prompt return of good heart action in sinus rhythm. When difficulty is encountered in aortic closure or insertion of the perfusion catheters and the anoxic period is prolonged, ventricular fibrillation occurs. However, when coronary perfusion is started, good myocardial tone is maintained, and there is no difficulty with electrical defibrillation. Early postoperative studies show varying degrees of myocardial depression, but this is transient and normal electrocardiograms are present after 1 week.

The major technical difficulties encountered have been preservation of the septal branch of the left coronary artery and closure of the aortic opening, especially when a short common coronary trunk is present. The septal branch originates posteriorly either from the main coronary trunk or from the anterior descending artery. It is a thin-walled vessel easily injured during dissection, and the resultant bleeding is difficult to control. Moreover, it may be encroached upon if the anastomosis is not performed carefully. Injury to the septal branch will predispose to arrhythmia and myocardial failure. Suturing of the friable aortic wall for large defects may result in a difficult problem with bleeding. Care must be exercised in this closure to prevent distortion of the aortic valve or annulus.

As an extension of this procedure, complete maintenance of the entire coronary circulation from a single left subclavian trunk is being developed (Fig. 9). This is accomplished by preserving a length of the internal mammary artery off the left subclavian artery and anastomosing this end-to-end to the divided right coronary artery as the main subclavian is anastomosed to the left coronary trunk. Thus, the entire coronary flow originates from the single left subclavian artery, and the entire coronary origin is transferred to the aortic arch.

This preparation extends the range of surgical and physiologic studies which are in process on survivors of the initial type of subclavian coronary transfer. The implications for placement of artificial valves in the ascending aorta are obvious.

SUMMARY

We have developed a technique for extending the length of the left coronary artery by transferring its origin to the left subclavian branch of the aortic arch. This is accomplished by end-to-end anastomosis between the left subclavian artery and the left coronary trunk during a short period of extracorporeal circulation with continuous coronary perfusion. Survival of animals for as long as 6 months provides a useful preparation for physiologic studies of coronary circulation and for surgical procedures on the aortic valve without danger of disturbing the coronary circulation.

SURGICAL DISORDERS OF THE BLADDER AND UMBILICUS OF URACHAL ORIGIN

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THE URACHUS forms a link between the fields of abdominal and urologic surgery, since it is a special narrowed segment of the bladder attached to the umbilicus. By utilizing the findings from 18 cases of urachal disorders, it will be shown how certain pathologic sequences follow from the anatomic structures remaining after embryonic development.

Although the 4 way grouping by Vaughan of "complete," "blind internal," "blind external," and "blind" has generally been followed, the cases seen in clinical practice are most logically segregated as follows: (1) congenital patent urachus (completely open) (Fig. 1); (2) vesicourachal "diverticulum" (open internal) (Fig. 2); (3) umbilical cyst and sinus (open external) (Fig. 3); and (4) alternating urachal sinus (alternating open).

EMBRYOLOGIC CONSIDERATIONS

Cullen has shown clearly the embryologic development of the umbilical structures. Early in embryonic life the bladder is a conical structure formed from the ventral cloaca (Fig. 4). At the umbilical cord it is continuous with the rudimentary allantois.

Before birth, the apex of the bladder narrows to form the urachus. The urachus embryologically is part of the bladder, and the allantois contributes nothing to its composition. A structure 2.5 centimeters long at birth (Fig. 5), the urachus is drawn down as the bladder descends to the adult position, because of its continuity with the vesical apex (Fig. 6). According to the detailed researches of Begg (2, 3), the urachus usually terminates against one of the obliterated hypogastric arteries at a point one-third of the distance from the bladder to the umbilicus. Hammond and co-workers could identify 4 different types of urachal termination from a large number of dissections of fetal and adult specimens: group I, in which the urachus extends to the umbilicus—average length 12 centimeters; group II, in which the urachus merges with one umbilical artery—average length 6.4 centimeters; group III, in which the urachus merges with both arteries—5 centimeters long; and group IV, in which the urachus is regressive—average length 3.4 centimeters.

Luschke had previously demonstrated that the urachal lumen persisted and was made up of irregularly alternating dilated and narrow segments, all lined by modified vesical epithelium and covered with attenuated smooth muscle coats.

To understand urachal disease, the following embryologic facts must be understood: (1) the bladder is not a pelvic organ at birth but lies so high that its apex may almost reach the umbilicus (Fig. 7); (2) as the bladder descends into the pelvis, the portion of the bladder which constitutes the urachus normally descends with it, forming a 5 centimeter appendage at its apex in the adult (Fig. 6); and (3) the lumen of the urachus does not become completely obliterated. Consequently, patent urachus is principally a disorder of the neonatal period, at which time the bladder has yet to descend and the urachus has not been fully formed. Urachal cyst, on the other hand, occurs principally in the adult patient after descent and maturation of the urachus have taken place. In the adult, degeneration and bacterial growth are required in order to expand the lumen and form an infected

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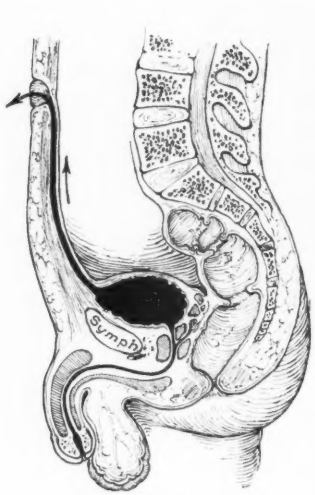
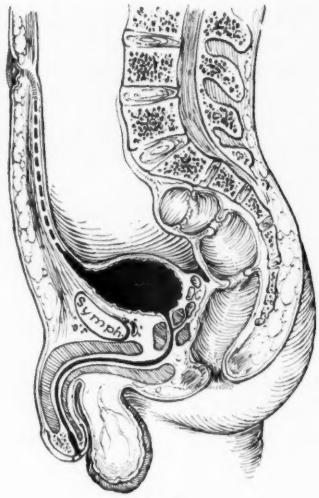


FIG. 1.



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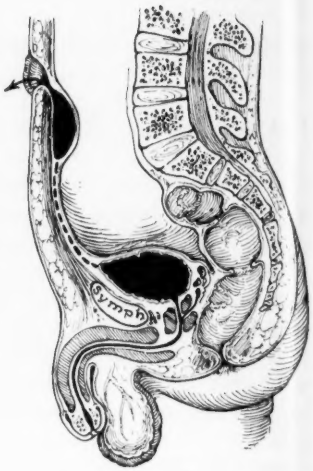


FIG. 3.

FIG. 1. Congenital patent urachus, complete.
FIG. 2. Vesicourachal "diverticulum," open internal.
FIG. 3. Umbilical cyst and sinus, open external.

cyst which can then open in either direction, to the umbilicus or to the bladder, or even in both directions at once (Table I).

CONGENITAL PATENT URACHUS

If the conical termination of the bladder persists so that a urachus does not form, the result has been termed a congenital patent urachus (Fig. 8b). In actuality, this form could better be considered as a congenital vesicoumbilical fistula and may be distantly related to vesical exstrophy. Simon and Brandeberry have chosen to call it "persistent fetal bladder," an expressive term but one which does not cover the variations of partial urachal formation. It can be shown that 3 stages exist: the first is persistence of the fetal bladder without descent, just mentioned; the second is persistence of the fetal bladder with descent but with prolongation of the apex; and the third is arrested closure of the urachus in spite of normal vesical descent (Fig. 8a). All are forms of congenital patent urachus.

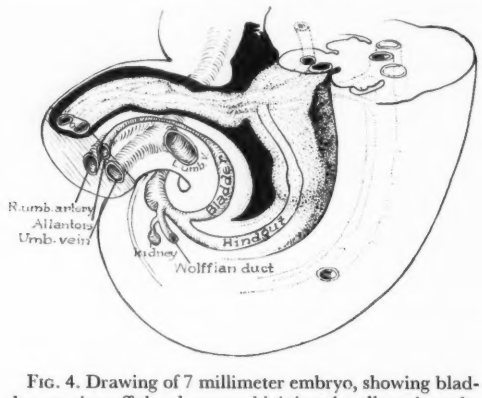


FIG. 4. Drawing of 7 millimeter embryo, showing bladder opening off the cloaca and joining the allantois at the umbilicus. The urachus will form by changes in the upper portion of the bladder, redrawn from Cullen.

Among animals, the disorder is most commonly seen in foals in which, significantly, cystitis is a common sequela. The umbilicus fails to heal and omphalophlebitis may also develop.

Urachal fistulas appear soon after birth (Table II). A few hours or days are necessary to allow the external, allantoic portion to slough. Considerable viable cord tissue often persists for unusually long periods. In this experience with 7 cases of patent

urachus, the shortest time for the appearance of urinary drainage was 5½ hours and the longest, 9 days. In some cases, drainage only occurred with abdominal pressure; but, in other infants, urine flowed from the umbilicus with each voiding, simultaneously with urethral flow. Caulton in 1757 described a patient who claimed to be able to urinate at will through the penis or umbilicus. In patients with intermittent leakage, resistance in the tract was presumably enough to hold at least 7 to 10 centimeters of water pressure, but not enough to contain 30 to 50 centimeters, the normal infant voiding pressure.

Associated obstructive anomalies were detected in 3 of the 7 infants. Complete studies were not made in the other 4 infants, but no suggestive symptoms or findings were detected. One infant (Patient 1) had bladder-neck obstruction with left hydronephrosis (Fig. 9) and another (Patient 3) had bilateral hydronephrosis, with absent abdominal musculature and right renal hypoplasia. A third infant (Patient 4) had a right renal filling defect due to cyst (Fig. 10).

Although the association of other anomalies has not been stressed by previous investigators, considerable supporting data may be drawn from reported cases. The first case of associated obstruction, reported by Ball in 1882, was in a child who died 3 months after closure by cauterization of a patent urachus. At autopsy, the bladder wall was found to be greatly thickened, and the ureters and renal pelvis were dilated. Presumably, the child had vesical neck obstruction, so that the vesicoumbilical fistula acted as a safety valve. The clinical implications seem obvious; surgical closure of a patent urachus in the presence of undetected lower tract obstruction could allow suppression of the remaining renal function.

In Herbst's tabulation of cases of urachal disorders up to the year 1937, there were 67 children under 15 years of age. Twelve of these children or 18 per cent had other genitourinary anomalies, usually those producing urethral obstruction. Many other single cases have been reported, including the first recorded occurrence of patent urachus, reported by Cabriolus in 1550, in an 18 year old girl who was treated by ligation of the fistula and dilatation of the urethra.

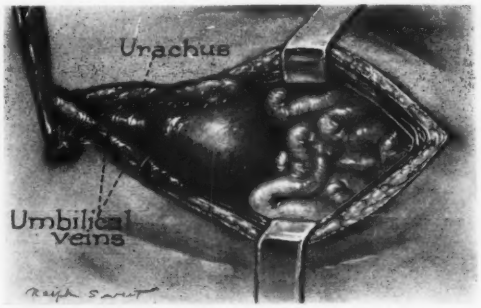


FIG. 5. Drawing of normal urachus exposed at operation for persistent umbilical remnant, showing relation of umbilical veins and bladder to urachus.

Diagnostic procedures in our series consisted of: pressure on the bladder to observe umbilical urinary flow (Patients 1 and 3); observation of leakage during micturition (Patients 1 and 2); and lateral cystograms

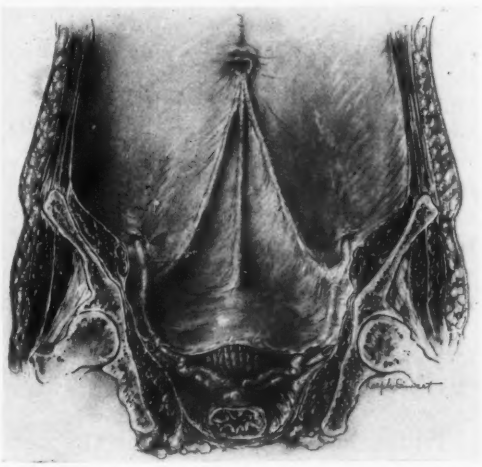


FIG. 6. Anterior abdominal wall in adult male, viewed from behind. In this case the urachus extends all the way to the umbilicus, lying between the obliterated umbilical veins—obliterated hypogastric arteries—rather than joining one or the other as is more common. This direct connection affords access for infection or urine from umbilicus to bladder.

FIG. 7. Lateral cystogram of normal newborn, showing anterior extension toward umbilicus and normal partial descent. Asterisk indicates site of umbilicus.

showing either a high bladder apex connected to the umbilicus (Fig. 8b) or a patent urachal tract (Patients 1, 2, and 4) (Fig. 8a). In Patient 1, a catheter could be passed into the bladder from the umbilical opening. In 3 others (Patients 5, 6, and 7) intravenous urograms or cystograms were taken which showed no communication between the bladder and umbilicus. The diagnosis in these infants was made by noting urinary drainage from the umbilicus. Methylene blue instilled in the bladder was helpful in establishing that the leakage was bladder urine.

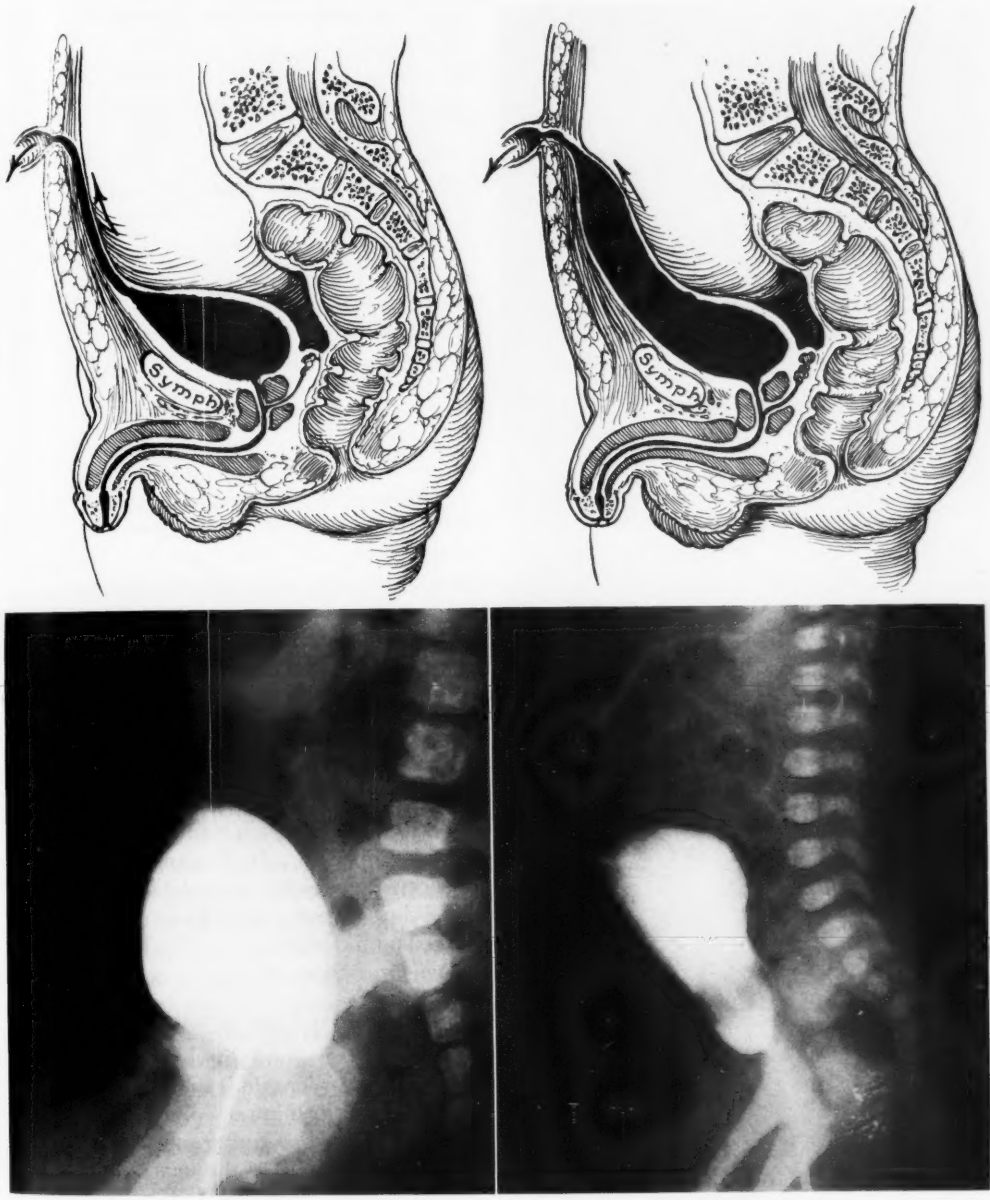
The urachal lesions must be distinguished from omphalitis and patent omphalomesenteric duct. A study of the upper gastrointestinal tract may be necessary.

Treatment was surgical excision in the 5 cases in which operation was possible. Of the 2 instances in which operation was not performed, the infant died 24 hours after birth in one and the mother "didn't want her child to go through life without a navel" in the other. Follow-up observation in this second case has not been possible. The umbilicus with the remnants of the cord was dissected in each patient operated upon, and the attenuated bladder dome was removed either without entering the peritoneum, in 3 cases, or by excising a strip of peritoneum, in 2 cases. The dome of the bladder was usually closed in layers with chromic catgut, although in Patient 7, the urachus was merely clamped and tied where it joined the bladder. Drainage was provided since infected tissues are common. In these infants, the umbilical vessels were barely obliterated and the periumbilical tissue was very friable, hence extreme care had to be used to avoid injury to the vessels. Bleeding in such cases is difficult to control.

Many types of treatment have been utilized in the past, but excision has been shown to be the best therapy. Of 100 patients reported by Nix and associates, excision was carried out in 43, either extraperitoneally or intraperitoneally. One death occurred with the latter approach. However, of the 13 tracts which were cauterized, 6 remained patent, and carcinoma developed in 3. There were 5 deaths among the

TABLE I.—FACTORS IN URACHAL DISEASES

Patient No.	*Diagnosis*	*Cause*	*Usual age*	*Urinary symptoms*
1, 2, 3, 4, 5, 6, 7	Congenital patent urachus	Failure of vesical descent and urachal regression	Infant	Umbilical urinary fistula
8, 9	Vesicourachal "diverticulum"	Dilatation of urachal stump from vesical neck obstruction	Adult	Usually none except from obstruction itself
10, 11, 12, 13, 14	Umbilical cyst and sinus	Infection in persistent urachal remnant	Adult	Umbilical sinus and granuloma
15, 16, 17, 18	Alternating urachal sinus	Infection in persistent urachal remnant	Adult	1. Recurrent umbilical sinus alternating with recurrent vesical infection 2. Occasional urinary fistula



a b

FIG. 8. a, Undescended bladder with communication with umbilicus—nonformation of urachus (Patient 4). b, Normal descent of bladder with persistent patency of urachus (Patient 2).

21 infants who received no treatment at all.

Pathologic sections of the present cases showed a tube composed of smooth muscle resembling normal bladder muscle, with an increase in connective tissue, and an epithelial lining (Fig. 11).

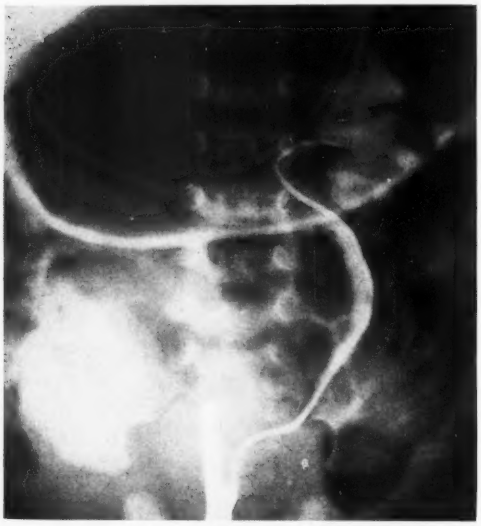


FIG. 9.

FIG. 10.

FIG. 9. Retrograde pyelogram showing congenital hydronephrosis due to ureteropelvic junction obstruction in case of patent urachus (Patient 1).

FIG. 10. Retrograde pyelogram showing congenital intrarenal simple cyst, probed at operation, in case of patent urachus (Patient 4).

TABLE II.—PATENT URACHUS

Patient No. Sex	*Age when drainage was noted*	*Associated anomalies*	*Treatment*	*Result*
1 M	9 days	Bladder neck obstruction and left hydronephrosis	Excision at once	Cured
2 F	4 days	None (IVP was not done, but no reflux or trabeculation found on cystography)	Excision at once	Cured
3 M	4 days	Hydronephrosis, absent abdominal musculature	None (autopsy)	Died in 24 hours without treatment
4 F	1½ hours	IVP showed right renal tumor (cyst)	Excision at once	Cured
5 M	"At birth"	None (IVP normal)	None	No follow-up
6 F	"At birth"	None? (cystoscopy normal, no residual urine)	Excision, age 3½ yrs.	No follow-up
7 M	"At birth"	None, recurrent pyelonephritis for 10 years	1. Attempted fulguration 2. Excision	No follow-up

The complication of infection of the cord remnants leads to septicemia or peritonitis and has been the usual cause of death in the past. One of the reasons for excising the urachal umbilical remnants rather than waiting for separation and obliteration is to avoid omphalitis. In Patient 1, a Staphylococcus aureus infection delayed operation for 9 days. Staphylococcus aureus also produced a mild wound complication postoperatively in Patient 4.

VESICOURACHAL "DIVERTICULUM"

Instead of the urachus being open throughout its length, it may open only into the bladder, forming a "diverticulum."

The etiology is apparent from the fact that the lower end of the urachal canal terminated freely with the interior of the bladder in from one-third to one-half of the cases studied histologically, but its lumen, being less than 1 millimeter in diameter, was so small that it rarely admitted dye, even when forced into it by direct injection. Since in these cases the urachus is technically patent,

TABLE III.—VESICOUMBILICAL "DIVERTICULUM"

Patient No. Sex	Age, yrs.	Symptoms	Treatment	Result	Comments
8 F	31	None (vesical neck obstruction)	Resection, vesical neck	Improved	No symptoms from urachus
9 F	57	None	None	Died, ruptured aneurysm	Incidentally found at autopsy

it is understandable that chronic obstruction at the vesical neck could cause it to dilate to form a "diverticulum." One case is reported by Mast and associates of a urachal diverticulum developing acutely after urethral occlusion by clots from a bleeding papilloma. The length of a vesicourachal diverticulum would be expected to be about 5 centimeters since this is the usual length of the urachus in the adult. Such have been our findings. In Patient 8, a 31 year old woman with a long history of recurrent infection, residual urine, and straining to urinate, cystourethrograms showed vesical neck obstruction with trabeculation and also demonstrated a 5 centimeter tubular appendage which filled from the dome of the bladder (Fig. 12) (Table III). She was treated by vesical neck resection with improvement. The diverticulum itself gave no symptoms and was not excised. Similar cases have been reported by others. One diverticulum even contained 1,500 cubic centimeters of urine.

In a second patient (Patient 9), probably representing the more common form since it differs so little from the normal situation, the urachal process, found incidentally at autopsy, consisted of a 5 centimeter tube with a flattened epithelial lining and abundant connective tissue interspersed with smooth muscle.

Calculi frequently have been found in the urachal lumen after Boyer's first report in 1787 (15) since the lumen may communicate with the bladder and since stasis would be expected to be present. No stones have been found in any of the cases described herein.

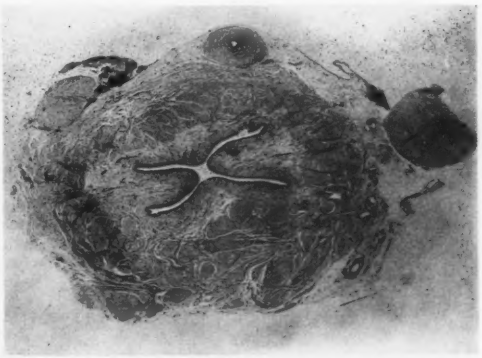


FIG. 11.

FIG. 12.

FIG. 11. Cross section of patent urachus (Patient 2) showing smooth muscle, increased connective tissue, and transitional cell epithelial lining. ×3.

FIG. 12. Cystogram showing urachal "diverticulum" at vertex of bladder (Patient 8).

UMBILICAL CYST AND SINUS

If the urachus opens only to the umbilicus, a urachal sinus may form.

Infected umbilical (urachal) cysts usually remain subumbilical. The first case was reported by Lawson Tait in 1883—quoted by Rees.

The incidence of cysts is usually greater in adults. Clinically, a urachal cyst appears as a red prominence within the umbilicus

FIG. 13.

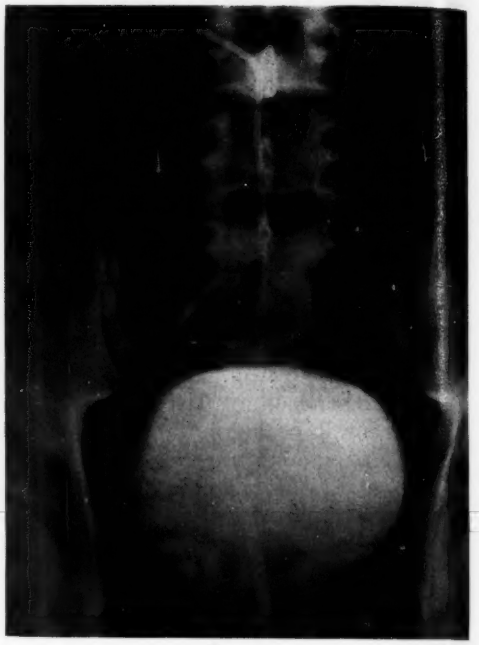


FIG. 14.

FIG. 13. Alternating urachal sinus in 2 year old girl (Patient 15) showing descended bladder. Catheter is seen in sinus.

FIG. 14. Alternating urachal sinus in 22 year old man (Patient 17). Catheter would pass only for a short distance down the sinus, but the tract discharged pus into the bladder.

which drains purulent material after application of hot compresses or after incision.

Symptoms consist of: (1) recurrent local infection, (2) acute infection with systemic effects, (3) lower abdominal tumor, and (4) gastrointestinal symptoms. In some cases there are no symptoms at all. Rarely, the symptoms may appear to represent a gynecologic problem. Systemic effects usually are mild, although reports of extension through the peritoneum show that fatal complications are possible.

TABLE IV.—UMBILICAL CYST AND SINUS

Patient No. Sex	*Age at onset of symptoms*	*Age at time of treatment, yrs.*	*Treatment*	*Result*	*Comments*
10 F	15 yrs.	15	Compresses	Well at age 22	
11 F	50 yrs.	50	Local	No follow-up	
12 F	4 mos.	1	Excision	Cured	
13 F	3 yrs.	3	Local	Well at age 6	
14 M	70 yrs.	70	Excision (segmental resection of bladder)	Cured	Urinary retention (BPH), with asymptomatic suprapubic mass

Hammond and co-workers, in studying the umbilicovesical fascia, found that this layer limits the spread of infection from the urachus, making umbilical (or vesical) drainage much more common than peritoneal extension.

Treatment was conservative in one 15 year old patient (Patient 10, Table IV). The lesion healed and had remained so when checked 7 years later. Two other patients (Patients 11 and 13) were also treated conservatively without sequelae. Two patients (Patients 12 and 14) had excision of the remnant with no further symptoms. Tissue sections in these cases showed inflamed fibrous sacs, without distinguishable epithelial lining or smooth muscle cells.

Whether excision is necessary in these cases has been questioned, although most

authors advise it, and scattered reports of the inadequacy of incision and drainage have appeared. Marsupialization was effective in 1 case. Further reasons for excision are reports of carcinoma arising in the urachal remnant, going back to Fischer's report in 1894. A total of 78 cases has been reported. Excision is probably indicated when symptoms persist for 6 months or more.

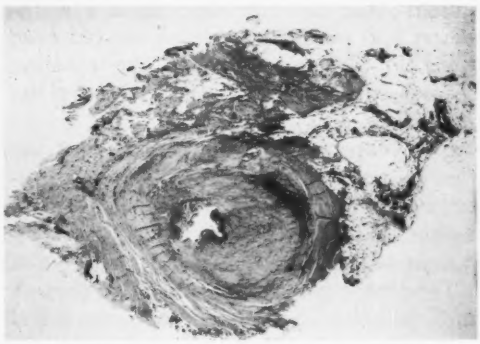


FIG. 15. Cross section of urachal sinus (Patient 17). Note marked chronic inflammatory changes with fibrosis. ×3.

ALTERNATING URACHAL SINUS

These cases comprise the most stimulating group from a urologic point of view because they combine umbilical symptoms and findings with those of disease of the urinary tract. The 4 cases discussed here are reported in greater detail in a report presently in preparation (10).

The etiologic factors are that the urachal canal remains as an epithelium lined tube, normally retracting from the umbilicus as the bladder descends. It may, however, remain attached at the umbilicus (group I of Hammond) and so be a potential connection between the bladder and the anterior abdominal wall. If infection arises in the desquamated cellular debris in the canal, it will follow the canal either to the bladder or to the umbilicus, or both. Begg does not believe that such a long tract persists, but rather that the infected cysts rupture into the fibrous tissue leading to the umbilicus. The fascia is suitably oriented for such a course. However, such a view is not in accord with the clinical observations in the cases reported here that the infection starts periumbilically as will be shown.

The occurrence has been principally in adults (Table V), the exception being a 2 year old child. There were no symptoms in any of the 4 patients for most of their lives. The first symptom was centered at the umbilicus, such as periumbilical pain or tenderness, redness, and purulent discharge. These symptoms continued for as long as 1 year before bladder disturbances occurred. These urinary symptoms were usually heralded by an exacerbation of the umbilical infection; the umbilicus became tender and red. In 1 case (Patient 5), incision and drainage were necessary. Often at the height of the disease at the umbilicus, the patient's temperature rose, urinary frequency, urgency, and nocturia occurred, and pyuria was detected by urinalysis.

Examination at this time revealed a red, slightly excoriated umbilicus, with surrounding areas of tenderness. A probe or ureteral catheter could be inserted into the sinus tract through the umbilicus in 2 of the patients (Patients 15 and 17). In the latter

TABLE V.—ALTERNATING URACHAL SINUS

Patient No. Sex	*Age at onset, yrs.*	*Age when seen, yrs.*	*Umbilical symptoms*	*Vesical symptoms*	*Treatment*	*Result*
15 F	1	2	At age 1, without urinary symptoms	At age 2, urinary infection with umbilical "abscess"	1. Drainage of "abscess" 2. Excision	Cured
16 F	17	18	Occasional thick drainage	Simultaneous cystitis	Excision	Cured
17 M	21	22	(Previous umbilical "milky" drainage) umbilical pain	Simultaneous urgency	Excision	Cured
18 F	22	22	Nausea, subumbilical mass	Pyelonephritis	Excision	Cured

patients, the catheter descended 8 centimeters and produced a desire to void even though it did not pass into the bladder. Urinalysis often showed pyuria and bacteriuria.

Cystoscopy revealed a red polyp at the apex of the bladder in Patient 18, a 6 centimeter bulging mass in Patient 16, and a scarred area with tenting at the dome in Patient 15.

Treatment was excision in each case. A midline incision was made about the navel to permit excision of the inflamed umbilicus and extended downward to allow dissection of the tract from the abdominal wall and peritoneum to the bladder. In 3 cases, the peritoneum was opened, once purposely. In all cases, the inflamed tract was densely adherent to the peritoneum, making dissection difficult. It was not always necessary to inject methylene blue since the fibrotic midline structures were easily identified and removed. A small portion of bladder muscle was excised in each case, but the mucosa was not opened. The vesical muscle was then closed in layers with chromic catgut for a watertight closure.

No further umbilical or vesical symptoms occurred in these 4 cases.

SUMMARY AND CONCLUSIONS

1. If the urachus does not form from the superior portion of the bladder, thus leaving the infant's normally high vesical apex open at the umbilicus, or if the urachus fails to contract upon its lumen, a congenital patent urachus is the result (7 cases).

2. The urachus normally extends upward from the bladder for a distance of 5 to 7 centimeters, and a microscopic lumen persists throughout life. It is open to the bladder in one-third of all people, although it is of such small caliber that urine does not enter it. Obstruction to the outflow of urine may rarely dilate the lumen, producing an asymptomatic vesicourachal "diverticulum" (2 cases).

3. Since the urachus is formed by constriction and atrophy of the apex of the bladder, since it retains its lumen, and since in a small group of individuals it may extend to the umbilicus, its involvement by any infection will subject the bladder to the possibility of infection. Among 9 patients with urachal infections, 5 had only a cyst or sinus limited to the umbilicus, but 4 also had involvement of the urinary tract (alternating urachal sinus). Excision provided definitive treatment in patients with persistent symptoms.

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POSTRADIATION URETERAL STRICTURE

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URETERAL OBSTRUCTION with resulting hydronephrosis is a common sequel to the progression of carcinoma of the cervix. Numerous studies utilizing autopsy material have indicated an incidence of ureteral obstruction varying from 65 to 85 per cent. Of these cases of ureteral obstruction, approximately 66 per cent are bilateral and 33 per cent unilateral. Compared with an autopsy series of noncarcinoma patients the incidence of hydronephrosis was 1.4 per cent unilateral and 0.6 per cent bilateral in distribution. A corollary of this condition is that renal infection and uremia be high on the list of causes of death of patients with carcinoma of the cervix, and de Alvarez has indicated that 40 per cent of such patients succumb from these complications. Even more startling is a study of 124 autopsies by Austin and Sala. In attempting to determine the causes of death in patients with carcinoma of the cervix, they found nephrogenic sepsis in 71.9 per cent and uremia in 4.8 per cent, a total of 76.7 per cent of deaths due to renal complications.

Thus, a high degree of prominence has been accorded the urologic complications of carcinoma of the cervix and, indeed, all pelvic neoplasms. In the normal course of spread from the cervix, the tumor mass expands locally causing distortion of the base of the bladder with subsequent encroachment of the lower ends of the ureters and resulting urinary stasis. As the disease progresses, the adjacent tissues are invaded by a lymphogenous spread of the malignant cells or by a superimposed pelvic cellulitis with resultant hydroureter and hydronephrosis. There may be no urinary tract symptoms at the time, and unless the syndromes of uremia or urosepsis occur, the patient may not seek medical attention.

The advent of radiation therapy for carcinoma of the cervix led to a re-evaluation of the problem of ureteral obstruction. Early techniques of radium application resulted in high levels of radiation to the cervix and adjacent structures during short periods of time, often eliminating the neoplasm but causing severe injuries to the urinary and gastrointestinal tracts. In 1939, Howes and Strauss studied 100 autopsy cases of carcinoma of the cervix in which radiation had been given and reported, "In several of our autopsies which revealed marked ureteral fibrosis and stenosis, a thorough search failed to reveal carcinoma cells." Bugbee, in 1934, reported 8 cases in which nephrectomy was carried out after radiation treatment for carcinoma of the cervix. In some of these cases, radium alone was given and, in others, a combination of deep roentgen therapy and radium. The dosage was smaller than that currently in use and no injury to the bladder was noted. Four of these 8 patients died shortly after nephrectomy with widespread metastasis from carcinoma of the cervix. The remaining 4 patients lived a considerable period of time free of tumor. Bugbee thought that the early breakdown of the tumor tissue after radiation, with the rapid cicatrization which resulted, caused the early ureteral obstruction and accounted for the ureterovaginal fistulas which occurred in 3 cases.

A current report evaluates the prognostic significance of the intravenous pyelogram in patients in whom ureteral obstruction develops after radiation to the pelvis for carcinoma of the cervix and in whom pretreat-

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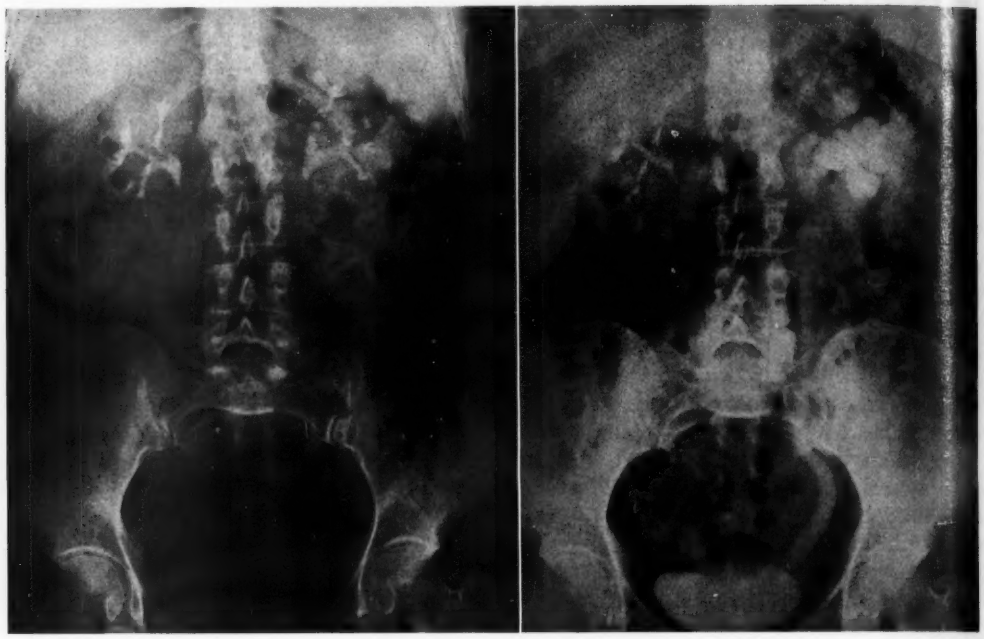

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FIG. 1. Patient 1. a, Normal pretreatment pyelogram. b, Excretory urogram taken 3 years after radiation therapy shows hydronephrosis and hydroureter on the left, with point of obstruction 3 centimeters from the left ureteral orifice.

ment excretory nephrograms were normal. If radiation is well planned and monitored, it is apparent that in the vast majority of patients posttreatment ureteral obstruction develops secondary to persistence and progression of tumor, and the ultimate prognosis is affected little by relief of the obstruction. Yet, occasionally, patients are encountered in whom ureteral obstruction develops after radiation therapy for carcinoma of the cervix and no neoplasm can be found. The incidence of postradiation ureteral fibrosis is not known. Since these patients have not been aggressively investigated, the reported incidence of 0.8 per cent of all patients with carcinoma or 6 per cent of those patients with urinary complications represents minimal figures for this lesion. Proper selection and treatment of these patients pose many problems for the surgeon as illustrated in the following.

REPORTS OF PATIENTS

PATIENT 1. A 56 year old, para 6, gravida 6 was first seen on 1 September 1953 with a complaint of a dull ache in the left lower quadrant of approximately 2 months' duration and also some pain, of less severity, in the right lower quadrant. In addition, there was some tenderness in the area of the rectum. In May 1953, an onset of tarry, black stools was noted. On at least 2 occasions, the stools became loose and watery. In July 1953, the patient experienced a feeling of fullness of the rectum, and the family physician was consulted.

A lesion of the cervix was found at examination of the pelvis. The only episode of vaginal bleeding occurred after this examination, and it was described as being bright red and persisting for approximately 24 hours. Patient had experienced anorexia and lost 14 pounds. Findings at physical examination were essentially normal with the exception of the pelvic examination. The cervix seemed to be completely replaced by an ulcerated cauliform lesion. The mobility of the cervix was limited, especially posteriorly and on the right. The lesion seemed to extend into the left posterior vaginal wall. The corpus uteri was normal in size, and there was nodularity of the parametrium on

c d

FIG. 1. c, Excretory urogram taken 2 months after ureteroneocystostomy. d, Reflux not demonstrable on cytogram.

the left side. The parametrium on the right side was less involved; the parametrial extension did not reach the lateral pelvic walls. Results of laboratory tests were within normal limits. Sigmoidoscopic examination demonstrated no intrinsic lesion of the lower bowel. However, there was induration of the rectovaginal septum. Papanicolaou examination of scrapings of the cervix demonstrated tumor cells. A biopsy of the cervix revealed epidermoid carcinoma. The carcinoma was classified clinically as stage II and 2 applications of radium were given followed by external radiation. The first radium application was given on 9 September 1953 and the second implant on 16 September 1953. The first application delivered 3,587 roentgens to point A. The second application was given so that 2,852 roentgens were given to point A. These applications were then supplemented by external radiation to 4 ports from 23 September to 22 October 1953. These were carried to a 2,000 roentgen air dose per each port. The lesion responded well to therapy, and follow-up in the clinic showed no tumor. In the fall of 1956, the patient experienced some discomfort in the left lower quadrant which disappeared at night but seemed to be aggravated by exercise. In early November 1956, the patient experienced shaking and chills which lasted for approximately 12 hours, but she had no fever. She was seen 5 November 1956 when a repeat pyelogram was performed which demonstrated a left ureteral stricture with left hydronephrosis. Pelvic findings at this time demonstrated the vagina to be closed, but surprising mobility of the cervix and uterus was found to be present as well as mild thickening in the parametrium; no evidence of viable tumor could be detected. On 23 November 1956, the lower end of the left ureter was excised, and the ureter was reimplanted into the bladder by a simple fish mouth technique. The resected ureter revealed marked fibrosis on microscopic sections. A splinting catheter was used and removed on the fifth postoperative day. The postoperative course was satisfactory, and the patient was discharged on 11 December 1956. A repeat pyelogram demonstrated the upper urinary tract to be normal, and follow-up examination failed to show any evidence of tumor.

PATIENT 2. A 49 year old, para 1, gravida 2 was admitted to the hospital in March 1950 because of intermenstrual spotting since January 1950. At biopsy, prior to admission, epidermoid carcinoma of the cervix had been established. The neoplasm was classified as International stage II because of slight parametrial thickening on the left. The pretreatment intravenous pyelogram was normal. In March and the end of

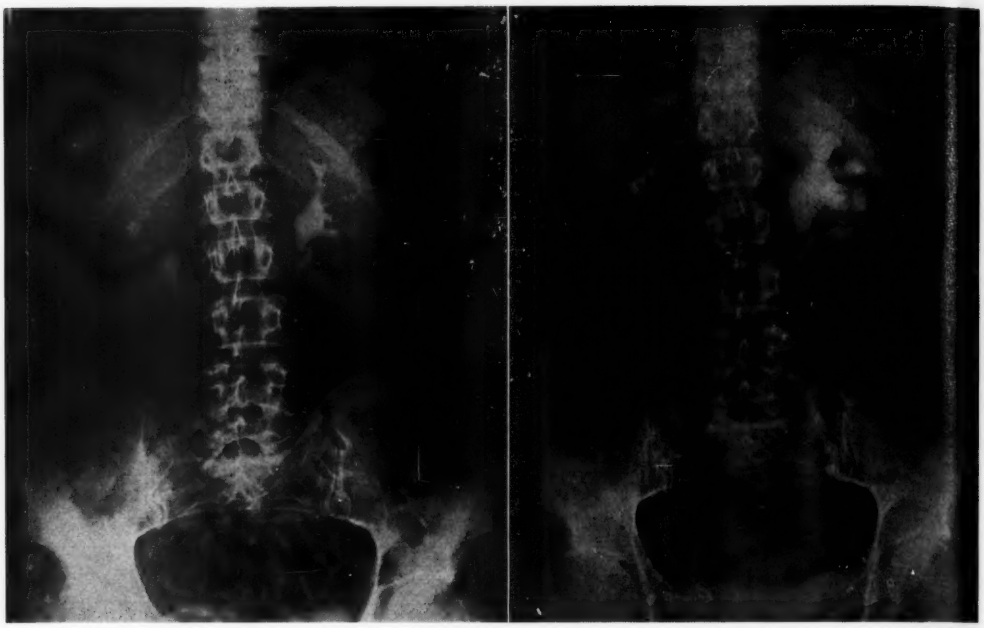

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FIG. 2. Patient 2. a, Normal pretreatment excretory urogram. b, Mild hydronephrosis and hydroureter indicated on left 4 years after treatment, secondary to fibrosis of the lower left ureter.

April in 1950, the patient received 1,800 roentgens of external radiation to each of 4 ports. Two radium applications were given in April with a total dose of 6,400 roentgens. After this treatment, there was a mild bladder reaction and 6 months later mild cystitis developed which persisted for several months. A normal pyelogram was obtained in December 1951. She was seen regularly until April 1954. On 1 August 1954, some mild dysuria developed, the pain radiating down the left side of the abdomen into the inguinal area on the left side. Examination revealed thickening of the left side of the parametrium extending to the lateral pelvic wall. An intravenous pyelogram demonstrated a mild hydronephrosis on the left side. Cystoscopy showed mild radiation cystitis. Retrograde pyelograms were taken which demonstrated narrowing of the lower third of the left ureter. Because no tumor could be demonstrated, clinically or roentgenographically, exploratory laparotomy was performed on 25 August 1954. There was marked induration of the parametrial area of the cervix, but no neoplasm was found upon frozen section. The uterus, cervix, fallopian tubes, ovaries, a portion of the lower left ureter, and the left side of the bladder were removed in a block dissection. Simple fish mouth type reimplantation of the left ureter was performed, and the bladder was closed. Examination of the specimen removed showed no evidence of neoplasm and diagnosis was radiation effect. Since that time, the patient has been under observation without evidence of tumor. On 1 March 1957, an intravenous pyelogram was taken and the results were negative.

PATIENT 3. A 41 year old, para 7, gravida 7 was first seen on 2 November 1952 with chief complaints of pain in the left lower quadrant and dyspareunia. The pain and irregular vaginal bleeding had been present for 2 years. Pelvic examination revealed an ulcerated lesion of the cervix which proved to be epidermoid carcinoma upon biopsy. The cancer was classified as International stage I since there was no evidence of extension from the cervix. The first radium application was on 3 November 1952, with approximately 3,565 roentgens delivered to point A. A second implant was made on 14 November 1952 with 4,450 roentgens reaching point A. No external radiation was given. The patient did well until January 1954, at which time she experienced pain in the right flank and right upper quadrant. An intravenous pyelogram demonstrated hydronephrosis on the right, secondary to obstruction near the right ureterovesical junction. The right kidney was palpably enlarged, movable, and slightly tender. The cervix was small, and there was no evidence of tumor. An indefinite mass was present in the parametrium on the right side. On 2 February

1954, abdominal exploration revealed a stricture at the right ureterovesical junction. Frozen section of tissue from this area revealed no tumor. The lower portion of the right ureter was resected, and a simple fish mouth ureteroneocystotomy was performed. The results of the last pyelogram obtained at this hospital on 28 August 1956, were within normal limits. To date there has been no recurrence of the tumor.

PATIENT 4. A 63 year old, white, para 2, gravida 2 was admitted to the hospital on 6 April 1959 because of postmenopausal bleeding of 8 months' duration. Biopsy of the cervix prior to admission had demonstrated epidermoid carcinoma. Intravenous pyelograms were within normal limits; however, there was extension of the neoplasm into the vaginal vault. There was no evidence of parametrial extension. This lesion was classified as an International stage II carcinoma of the cervix. Two radium applications were performed, one on 9 April 1959 and another on 20 April 1959. A total dose of 8,000 roentgens was given to point A. External radiation by conventional 4 port delivery was performed with approximately 2,000 roentgens in air given to each port. In June 1960, the patient noticed a heavy feeling in the lower part of the abdomen and some bleeding from the rectum. Vaginal examination performed under anesthesia demonstrated partial stenosis of the upper vagina as well as small nodules in the lateral vaginal wall. The cervix was freely movable. Biopsy of the cervix and needle biopsy of the parametrial tissue failed to reveal tumor. Cystoscopy demonstrated radiation changes. Intravenous pyelograms demonstrated a hydronephrosis on the right side. Retrograde pyelograms indicated narrowing of the right ureter at a point approximately 16 centimeters from the right ureterovesical junction. Sigmoidoscopic examination demonstrated only radiation change in the bowel. Because of the hydronephrosis and failure to demonstrate residual tumor, laparotomy was performed on 20 July 1960. Marked fibrosis with stricture of the right ureter was discovered. The stenotic ureter was excised and an Ockerblad flap brought up to the right ureter which was implanted into the flap. Histologic examination of the resected ureter revealed marked radiation fibrosis. Postoperative intravenous pyelograms have shown a return to normal. Cystogram failed to show any reflux into the right lower ureter. At present, the patient is living, well, and without evidence of tumor.

c

FIG. 2. c, Normal pyelogram taken 1 year after reimplantation of left ureter.

DISCUSSION

The pathway of obstruction of the ureter in untreated patients is by local extension and lymphatic metastasis. In the untreated case of carcinoma of the cervix, the ureteral obstruction is almost always due to the tumor itself and manifests as carcinomatous invasion of the ureteral wall or by a surrounding mass of carcinoma without any direct invasion of the ureter itself. In some instances, the accompanying inflammatory parametritis may be the cause of the obstruction.

When carcinoma of the cervix is treated by radiation, the nature of the obstruction is less well defined. Initially, the patient may demonstrate a transient hydronephrosis which clears rapidly. This is probably caused by edema, secondary to radiation. This feature has been observed in several of our patients and usually appears 3 weeks after the initial radium application. Obstruction which persists must be considered to be secondary to carcinoma or fibrosis.

The tumor may excite a pronounced desmoplastic reaction, with resultant obstruction. Cosbie studied the importance of secondary infection. By taking routine cultures from the cervix of 243 patients with cervical carcinoma, he found that in 25 of 47 patients with positive hemolytic streptococcus cultures subsequent complications

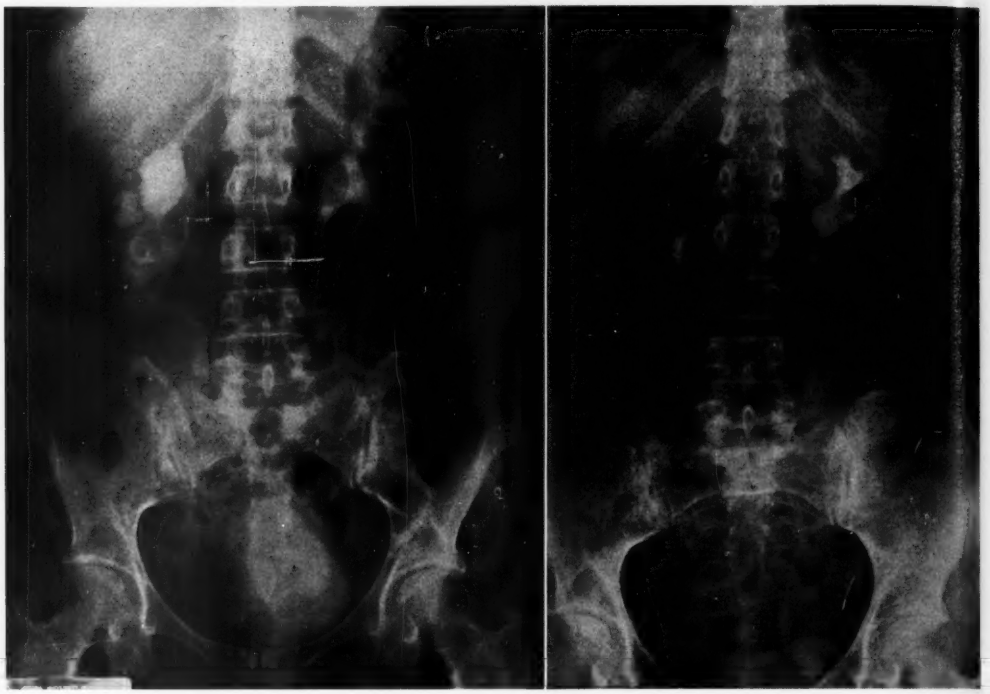

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FIG. 3. Patient 3. Pretreatment pyelograms taken in 1949 were reported to be normal. a, Intravenous pyelogram taken 2 years after treatment shows marked hydronephrosis and hydroureter on right. Point of obstruction cannot be seen. b, Excretory urogram taken 2 years after reimplantation of right ureter shows return to normal.

developed consisting of pyometra, cellulitis, thrombophlebitis, pelvic abscess, peritonitis, and septicemia. In another series of 176 patients, anaerobic cultures were obtained with 72 positive cultures. In 32 patients with positive anaerobic cultures inflammatory complications developed later. Of the 129 patients in whom the cultures were negative some sort of inflammatory complication developed in only 20 per cent. It is probable that, in a few cases, the fibrosis observed around the ureters and elsewhere in the pelvis was the result of the natural healing process following radiation inhibition of the tumor and resolution of the associated parametritis.

In instances in which the ureteral wall is invaded by tumor or the surrounding ureteral sheath is invaded, radiation induced tumor necrosis is followed by fibrosis which accounts for some of the cases of ureteral obstruction. Some disruption of the normal layers of the ureter should be present when the ureteral wall is invaded, and this was not observed in any of our cases.

The question of direct radiation injury to the ureteral wall has been studied by several investigators. Martin and Rogers were able to produce hydronephrosis in dogs by the direct application of 75 milligrams of unfiltered radium to the ureteral wall. More recently, Guye and O'Shea were able to produce ureteral strictures in dogs by the direct application of radioactive strontium. Only transient hyperemia and edema were found with a dosage of 300 roentgen equivalent physical (rep) and the ureters were normal in 10 to 30 days. With 700 rep

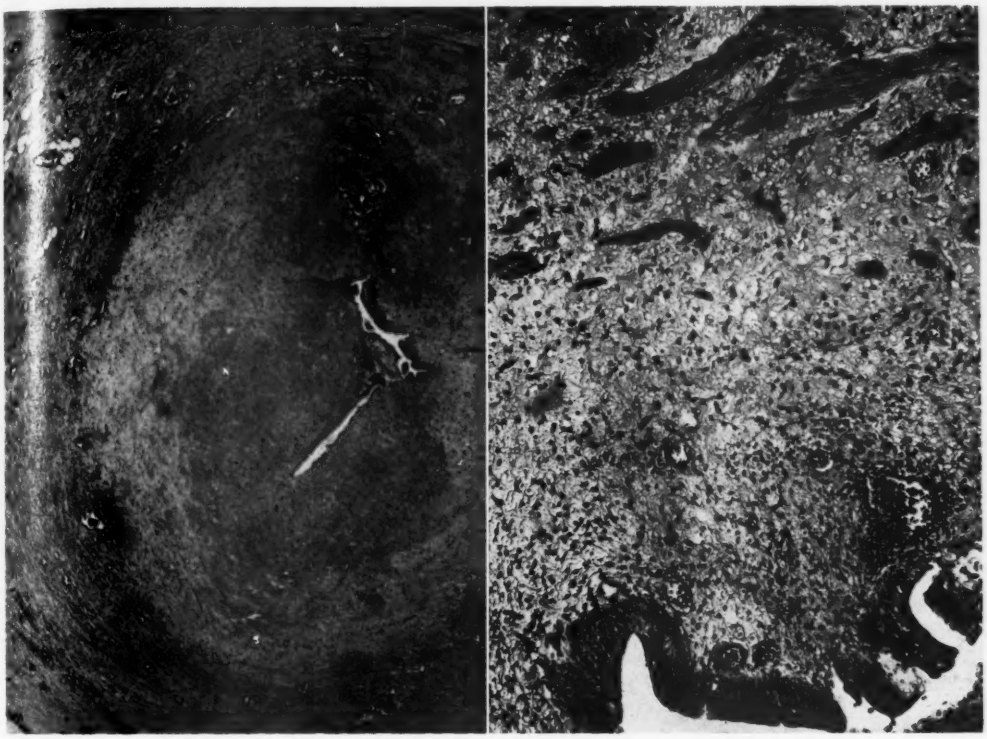

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FIG. 4. Patient 4. Sections of resected ureter show marked radiation change characterized by fibrosis, necrosis, edema, endothelial proliferation, and leukocyte infiltration. a, Low power magnification shows marked thickening of lamina propria. b, Higher power magnification indicates details of changes in lamina propria.

the maximum hydroureter was seen in 1 to 4 weeks after which time the process subsided for from 7 to 8 weeks, after which a secondary hydronephrosis developed. With 1,500 rep, the hydronephrosis was progressive from the start. Thus, development of direct radiation fibrosis has diminished with refinement of techniques of therapy. The ureter receives a relatively high dosage which, when coupled with the associated parametritis, results in fibrosis and possible stricture.

The presence of ureteral obstruction does not indicate a tumor in all cases. A careful program of pretreatment and postradiation pyelographic evaluation is essential. When obstruction occurs after radiation therapy, biopsies from the cervix and parametrial tissues are performed as well as roentgenograms of the chest and cystoscopy. In indicated cases, retrograde pyelograms using radiopaque media with 2 per cent neomycin are taken. If, at the conclusion of these examinations, no tumor is demonstrable, then abdominal exploration is carried out.

The most frequent site of the stricture is 4 to 6 centimeters from the ureteral orifice, where the ureter passes through the broad ligament. This is the area in which parametritis is the greatest, tumor invasion most often occurs, and in which a high level of radiation is received. Fibrous strictures are not confined to this area; for example, in Patient 4 the obstruction was at the pelvic brim. The mucosa of the ureter is smooth at the site of the obstruction and the area ap-

pears tapered, much as in idiopathic periureteral fibrosis.

Once the diagnosis is made, the management may be varied. Nephrectomy has been performed for unilateral lesions. With a potentially bilateral lesion, conservation of renal tissue is a requirement. Nephrostomy may be used as a diversionary procedure, but this, of course, does not restore normal drainage. Several instances of ureteral dilations have been reported in the literature. Examination of the amount of fibrosis present makes this procedure seem inadequate. Valk attempted ureteral dilation and stated that he was not able to bring about regression of the hydronephrosis in any instance.

In all of our cases, ureteroneocystostomy was performed with successful results. In 3 of the cases, the ureter was brought into the bladder by the split fish mouth technique. In Patient 4, an Ockerblad bladder flap was constructed. The site of obstruction is usually situated so that one of these procedures may be performed.

SUMMARY

Fibrotic strictures of the ureter can and do occur after radiation of carcinoma of the uterine cervix. Careful observation, postradiation pyelograms, and an intelligent selection of patients for operation will result in a rehabilitated patient.

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PNEUMOPERITONEUM IN INFANCY

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THE OPPORTUNITIES for differential diagnosis of surgical diseases in infants under 1 year of age, particularly if pneumoperitoneum has been a presenting factor, have been infrequent. Careful correlation of operative and postmortem data with clinical and roentgenologic findings has made it possible to identify preoperatively the site and nature of most of the obstructions, masses, and abnormal communications which occur in the newborn. However, the numerous conditions which give rise to pneumoperitoneum in infancy have been less well studied.

Free air in acute abdominal conditions of infants is uncommon, and the difficulties encountered in diagnosis and treatment allow for little complacency upon the part of surgeons entrusted with their care.

The series of patients presented reflects the problem of pneumoperitoneum as encountered on the pediatric surgical service of a large charity hospital. Common to all was a preoperative roentgenologic diagnosis of pneumoperitoneum (Fig. 1), with little else in the way of clinical or laboratory findings to suggest the site of origin.

PATIENT MATERIAL

Included in this study are 15 infants with pneumoperitoneum of uncertain origin prior to laparotomy. They represent 1.6 per cent of all infants less than 1 year of age undergoing abdominal surgery in the hospital during a 7 year period and were encountered in the 57,500 total admissions to the pediatric hospital. The pathologic findings are summarized in Table I. The recorded cause of death was established either on the basis of autopsy examination or on the opinion, after personal observation, of one or more of the authors.

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ETIOLOGY AND CLASSIFICATION

The sites of perforation in this series were gastroduodenal in 6 patients, jejunoileal in 5, and in the colon in 4.

Any classification on the basis of etiology is subject to question. The 6 gastroduodenal perforations make up the largest group. One instance of perforation proximal to a point of mechanical obstruction was encountered. In this infant, a linear tear of the anterior wall of the greater curvature of the stomach was the result of duodenal obstruction by the superior mesenteric vessels. The remaining 5 cases are termed "idiopathic" to indicate the absence of an obvious mechanical factor in causation, although at operation the pathologic findings suggested acute peptic ulceration. Two of these ulcers were gastric in location, and the remaining 3 ulcers occurred in the first portion of the duodenum.

There were 5 instances of jejunoileal perforation, 2 of which were proximal to the site of complete small bowel atresia. Severe mechanical distention was, undoubtedly, a major factor in perforation, but an additional element of vascular compromise as a result of volvulus was present in 1 case. In the remaining 3 patients, neither the operative findings nor postmortem examination established a clear-cut cause of the perforation in the terminal ileum. Two of the 3 infants were premature, and the irregular peristalsis, deficient intestinal musculature, and susceptibility to infection so frequently seen in this group may have been contributing factors.

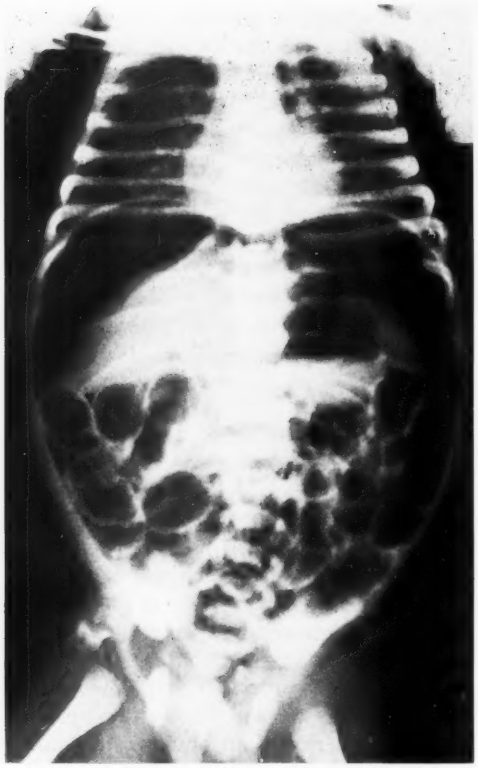

FIG. 1. Preoperative roentgenogram of the abdomen in the upright position demonstrating the presence of pneumoperitoneum.

In the colon group, with the exception of 1 patient in whom there was a traumatic injury from a rectal thermometer, etiology was equally baffling. In 2 patients, the involvement of the cecum at operation suggested obstruction of the distal portion of the colon with cecal blowout, but at autopsy, neither mechanical nor functional cause was found.

In the fourth patient, the pneumoperitoneum was, undoubtedly, the result of pneumatosis cystoides intestinalis involving the cecum and ascending colon. A gross perforation was not identified, the child survived, and etiologic proof is lacking. There was no evidence of Hirschsprung's disease in the 3 patients whose perforation was considered idiopathic.

DIAGNOSIS

In this series, certain clinical and roentgenologic considerations in the diagnosis of pneumoperitoneum became apparent and deserve emphasis. These children, with rare exceptions, appeared acutely ill, with distention and vomiting. They seldom vomited bile, however, and thus the need for surgical consultation might be overlooked. It is essential that roentgenograms, with the patient in both supine and upright positions, be taken promptly. In 1 infant with a perforated peptic ulcer (Fig. 2), the presence of free air was suggested in the supine position, but the more striking and diagnostic qualities in the upright view were obvious. Smaller collections of free air may be missed if examination is limited to the supine position. In another patient in whom serial roentgenograms were taken only in the supine position (Fig. 3), considerable controversy arose over the nature of the "distended loop of bowel." Exploration proved pneumoperitoneum and not distended intestine.

On occasion, roentgenologic study may suggest the etiologic factor responsible for perforation, particularly when a mechanical obstruction exists. Figure 4 is an interesting sequence of roentgenograms obtained on a 10 day old child admitted for suspected upper gastrointestinal obstruction. The first roentgenogram made on admission showed a dilated stomach with an air fluid level. Distal obstruction was suggested but there was no free air. Shortly after admission the child's condition worsened and a repeat film 4 hours later showed obvious pneumoperitoneum. At operation, there was a gastric tear proximal to a superior mesenteric vessel obstruction of the duodenum. Duodenojejunostomy and suture repair of the stomach were carried out. Five days later, when the child appeared well on the way to recovery, roentgenolography showed rapid and complete absorption of the free air.

TREATMENT

Once free air in the abdomen is detected, the need for surgical intervention is seldom

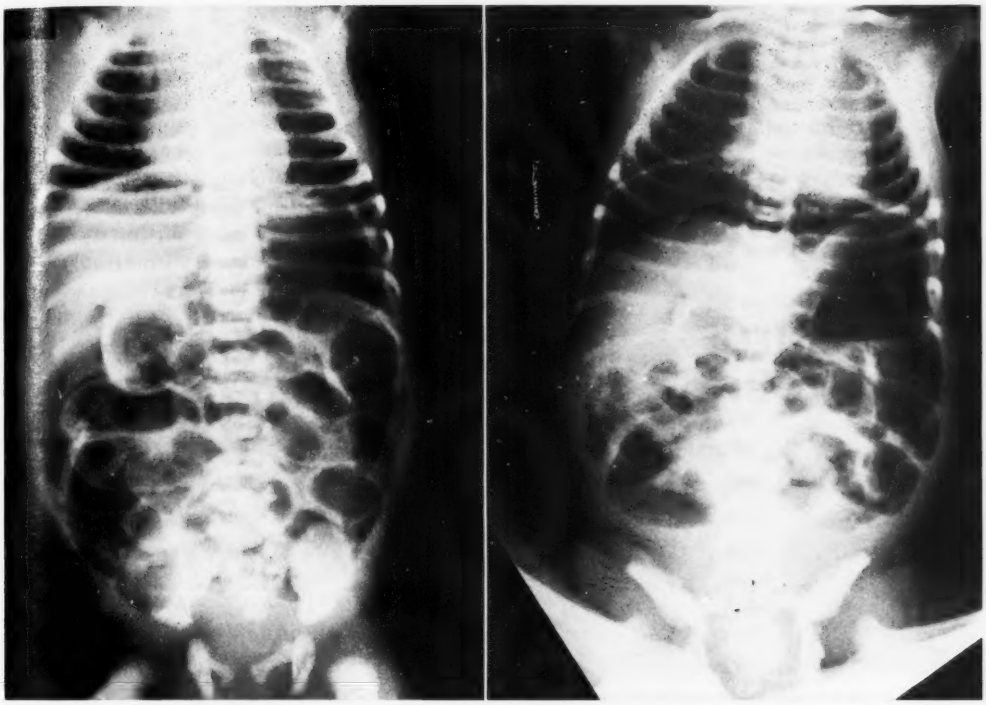

FIG. 2. Supine and upright views of infant with perforated duodenal ulcer.

questioned. In 14 of the 15 patients, there was rapid deterioration following recognition of the pneumoperitoneum, and emergency laparotomy was performed in an attempt to arrest the relentless progression of peritonitis. In only 1 infant was the advisability of laparotomy questioned. This patient remained in surprisingly good health over a 24 hour period of observation, in spite of large and continually increasing amounts of free air in the abdomen evident on physical and repeated roentgenologic examinations. Pneumoperitoneum and localized pneumatosis cystoides intestinalis were present at laparotomy, but the absence of a demonstrable leak and little evidence of peritonitis, undoubtedly, accounted for his clinical condition and survival.

At laparotomy the surgeon is confronted with a threefold task: identifying the site of perforation, repairing it, and then attempting correction of underlying etiologic factors. The problems encountered may vary from the insignificant to the insurmountable but will, in most instances, respond to a systematic approach based upon established principles of general and pediatric surgery.

Identification of the site of perforation represents the first and often the most difficult phase of surgical management. The use of a long right paramedian incision is strongly recommended. Current enthusiasm for transverse incisions in pediatric surgery would appear ill advised for infants with pneumoperitoneum.

If preliminary exploration of the usual sites of perforation (Fig. 5) is unrewarding, prolonged and poorly tolerated manipulations may be avoided by recourse to 2 readily available adjunctive procedures. First, the instillation of sterile methylene blue dye down the indwelling nasogastric

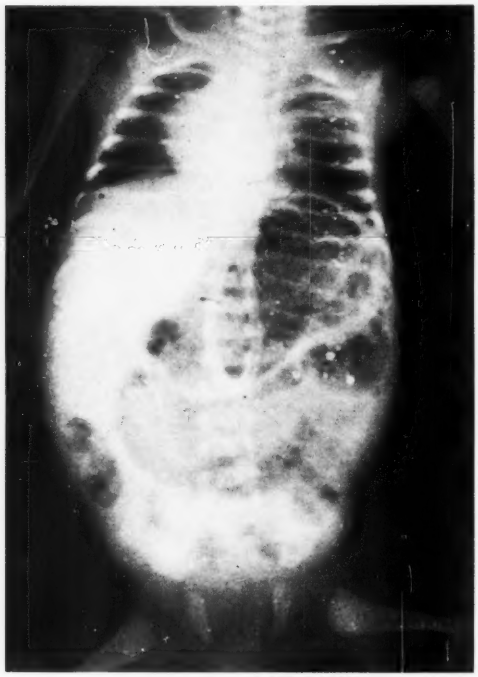

FIG. 3. Appearance of pneumoperitoneum in infant in supine position. Free air beneath gastric air bubble suggests a distended loop of bowel.

catheter will usually identify the site of upper gastrointestinal leakage. The telltale staining of the peritoneal cavity will quickly establish a perforation of the posterior portion of the gastric wall that is so easily missed with disastrous consequences. If this procedure fails, the abdominal cavity should be filled with warm saline solution, and by gentle compression of the distended intestines the escape of small air bubbles may be sought much as the gas station attendant seeks the site of a leakage in a flat tire.

Should both of these methods fail to localize the site of perforation, the surgeon must consider the possibility of minute air leakage from an area of pneumatosis cystoides intestinalis and carefully palpate the entire gastrointestinal tract for areas of telltale crepitation. Although self sealing of small perforations can undoubtedly occur, the tragic consequences of undetected perforations reported by Linkner and Benson require the meticulous enactment of these procedures before terminating the laparotomy.

Once the pneumoperitoneum is identified, the repair is based largely upon established principles of intestinal surgery and the pathologic conditions encountered. An ever present danger is that the repair may compromise the tiny intestinal lumen. While gastric perforations are readily sutured in layers, the use of a free or attached omental graft appears satisfactory for duodenal perforations due to peptic ulceration. Idiopathic perforations of the terminal ileum tax surgical judgment and skill. If closure seems indicated, a single layer of interrupted fine silk sutures is usually all that is accommodated regardless of the relationship of the closure to the long axis of the bowel. Where sound surgical judgment dictates, the simplest and most effective technique is exteriorization of the perforated ileum or colon through a separate muscle-splitting incision. The necessity for a snug closure and use of a few interrupted sutures between the exteriorized bowel and peritoneum, as emphasized by Swenson, deserves re-emphasis. When feasible, colon perforations are best exteriorized, but attempts at repair without exteriorization should be protected by a proximal colostomy.

If the pathogenesis remains obscure, the correction of underlying etiologic factors may be difficult. In most instances of perforation proximal to an area of mechanical obstruction, either resection or bypass of this region will suffice. In cases of cecal perforation, careful inspection of the entire colon is accomplished with difficulty and will not conclusively exclude functional obstructions such as may occur with aganglionic megacolon, as mentioned by Lewis. Spontaneous intestinal perforation secondary to Hirschsprung's disease was not encountered. In 1 instance, the site of perforation was small and immediately adjacent to the ileocecal valve. The perforation was

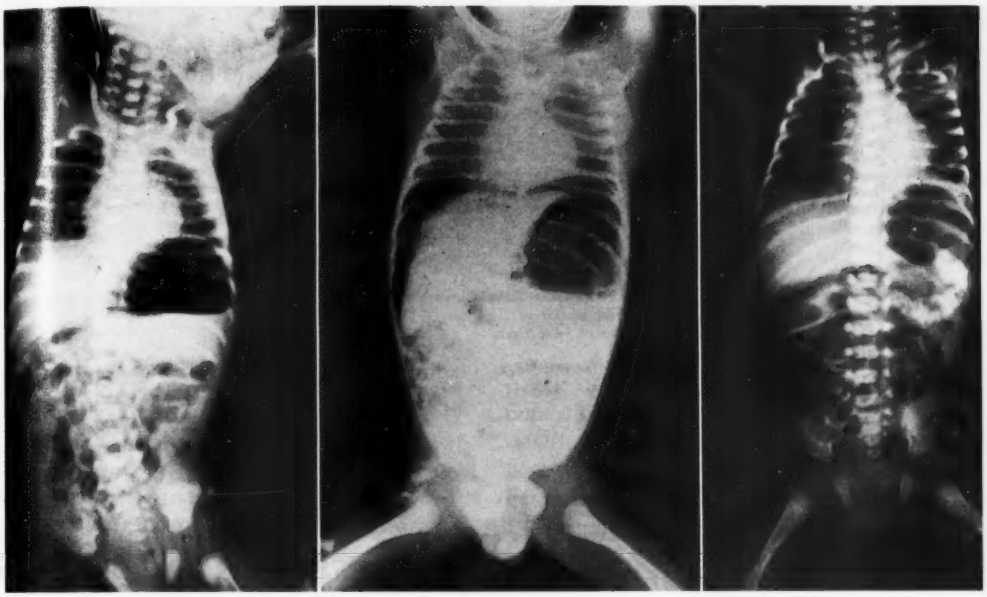

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FIG. 4. Sequence of roentgenograms in infant with perforation proximal to duodenal obstruction. a, Prior to perforation with air fluid level in distended stomach. b, Four hours later—pneumoperitoneum. c, Fifth postoperative day—air absorbed and anastomosis functioning.

closed, and colonic decompression was provided by the use of catheter appendicostomy. Insertion of a catheter through the wall of a distended and friable cecum may prove difficult, whereas the ready availability of the appendix and the ease with which fixation to the abdominal wall is attained render appendicostomy a worthwhile substitute for cecostomy when tube decompression seems desirable.

Finally, the use of copious warm saline irrigations of the contaminated peritoneal cavity and incision, adequate blood and plasma replacement, and a careful abdominal closure with interrupted fine wire are additional measures of value in the surgical care of these infants with gross peritonitis.

RESULTS

Only 2 children in the series survived the immediate postoperative period. One 3 day old infant had a perforated duodenal ulcer that was successfully closed with a free omental graft. Recent study of the patient at the age of 1 year shows no evidence of further gastrointestinal difficulty. A long term evaluation of this child's gastric function and acid peptic activity is anticipated.

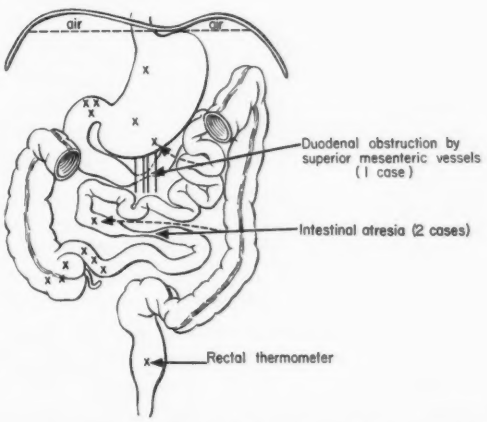

FIG. 5. Sites of perforations in 15 cases of pneumoperitoneum in infancy.

TABLE I.—SUMMARY OF PATIENTS

Patient No. *Sex* *Race*	*Weight* *Age at onset*	*Physical findings*	*Pathology*	*Surgery*	*Clinical course*	*Autopsy findings*
1 M N	6 lbs. 2 ozs. 3 days	Distention, tympany, free air	Perforated duodenal ulcer with fibrinous adhesions	Closed with omental graft	Wound infection; feeding problem; GI x-ray films normal	
2 M N	4 lbs. 5 ozs. 6 wks.	Diarrhea with vomiting for 2 weeks; developed distention, paralytic ileus	Perforated ulcer, superior anterior border of 1st part of duodenum; peritonitis	Closed with omental graft	Died 2 days postoperatively	
3 M N	4 lbs. 9 ozs. 5 days	Cesarean section; became distended on 5th day	Perforated ulcer, anterior surface of stomach; size 1 cm.	Closure in 2 layers	Died 2nd postoperative day	Atelectasis; peritonitis
4 M N	5 lbs. 7 ozs. 7 wks.	Diarrhea since birth; severe dehydration; improved after 3 wks. therapy, then became distended	Perforated duodenal ulcer	Closed with omental graft	Died 1st postoperative day	2 ulcers in duodenum; 1 perforated, closed surgically; septicemia; adrenal hemorrhage
5 F N	5 lbs. 16 ozs. 2 days	Cesarean section; biliary emesis; distended, icteric	Atresia of ileum with perforated atretic end ileum; gangrene 3 ft. of distal ileum secondary to volvulus	Resection and anastomosis	Died 1st postoperative day	Peritonitis; atelectasis; subdural hemorrhage
6 F N	2 lbs. 3 days	Distention	2 mm. hole in terminal ileum 1 in. proximal to ileocecal valve	2 layer closure of perforation	Died 2nd postoperative day	Massive atelectasis; nonspecific ileitis
7 M N	2 lbs. 11 ozs. 8 days	Double footling breech; septic amniotic fluid, vomited at 5 days	1 in. laceration of greater curvature of stomach; dilatation of duodenum as far as superior mesenteric vessels	Closure of laceration; duodenojejunostomy	Lived 5 days; vomited and aspirated	Gastric contents in tracheobronchial tree; anastomosis good
8 M N	1 lb. 3 ozs. 4 days	Abdominal distention	Perforated ileum 1 cm. longitudinal tear on antimesenteric border 4 in. above ileocecal valve	Exteriorized	Died 1st postoperative day	
9 M N	6 lbs. 8 ozs. 2 days	Abdominal distention; biliary vomitus	Colon dilated to sigmoid; perforation of cecum, pinpoint size	Closure of cecum and appendicostomy	Died 3rd postoperative day	Sclerema; localized pseudomembranous colitis; toxic hepatitis
10 M N	8 lbs. 4 days	Home delivery; no stool; distention	3 cm. ragged perforation of cecum	Exteriorized perforation	Died 1st postoperative day	No distal obstruction; ganglion cells found throughout colon
11 F N	6 lbs. 18 hrs.	Distended at birth; free air at 12 hours; intraperitoneal calcifications on x-ray; passed meconium plug	Perforations terminal ileum 200 c.c. fluid in peritoneum	Exteriorized	Died 1st postoperative day	Massive atelectasis; no evidence of obstruction or fibrocystic disease of pancreas
12 F N	2 lbs. 8 ozs. 8 days	Abdominal distention at 8 days; previously well	Perforated rectum; pelvic abscess (apparently thermometer)	Closure of perforation; proximal colostomy	Died 4th postoperative day	Peritonitis; septicemia
13 M N	3 lbs. 12 days	Abdominal distention; no stool	Atresia of jejunum with perforated ligament of Treitz	Resection of atretic jejunum; gastroenterostomy	Died 3rd postoperative day	Peritonitis; aspiration pneumonia

TABLE I.—SUMMARY OF PATIENTS—Continued

Patient No. Sex Race	Weight Age at onset	Physical findings	Pathology	Surgery	Clinical course	Autopsy findings
14 F N	9 lbs. 4 mos.	Diarrhea improving on neomycin; 2 days of abdominal distention, tympanitic hypoactive bowel sounds	Pneumatosis cystoides intestinalis on cecum	Exploration; no perforation found	Recovery with discharge 12 days postoperative; re-explored for adhesive bowel obstruction	
15 M N	5 lbs. 6 days	Admitted from home; umbilical bleeding, shock; became distended, vomited	Rent on greater curvature 1.5 cm. in diameter	Closed in 2 layers; gastrostomy	Died 1st postoperative day	Peritonitis secondary to hemolytic staphylococcus, coagulase positive

The second survivor was the child with pneumatosis cystoides intestinalis previously mentioned. The postoperative course was complicated by an episode of adhesive bowel obstruction requiring laparotomy but at present, 6 months after the initial operation, the patient is well.

The factors responsible for death in the remaining 13 cases are multiple and are shown in Table I. Delay in diagnosis would appear to be a major and an avoidable factor. While the incidence of prematurity weighed heavily against the chances for survival in many of these infants, the other nemesis of the pediatric surgeon, multiple anomalies, was not a problem.

DISCUSSION

The accumulated experiences recorded in the pediatric and surgical literature on pneumoperitoneum in infancy encompass a wide range of diverse pathologic entities. Attempts to summarize and classify the principal etiologic factors often fail because of the uncertainty which surrounds many reported cases. In addition, multiple factors may contribute significantly to the occurrence of a given perforation.

Pneumoperitoneum in many instances is the result of mechanical problems. In the gastroduodenal area, however, acid peptic digestion undoubtedly plays a major, if not an all important, role in perforation, although its full significance may be difficult to prove even at postmortem examination. Over a century ago Rokitansky associated peptic ulcers in the newborn with a "morbid condition of the vagus nerve and to extreme acidification of the gastric juices"—the currently acceptable concept of the pathogenesis of adult duodenal perforations. Partial confirmation of this view was provided by Miller in 1957; he demonstrated that in the newborn the gastric acidity is high and approaches that of an adult. Peak levels are seen in the first 2 days of life, drop thereafter, and remain low for the next 10 days.

Perforations of the ileocecal area remain of obscure pathogenesis. While mechanical obstruction is not an infrequent cause its demonstration at laparotomy or autopsy may be difficult. Algerty, Ziserman, and Schellenberger reported a case in which a firm meconium plug was expelled by an infant 48 hours after suture repair of an ileal perforation. Lewis reported instances in which the functional obstruction imposed by aganglionic Hirschsprung's disease resulted in perforation of the colon and emphasized that, unless this etiologic possibility was carefully investigated, it might readily escape detection in the newborn period.

In most instances, as in 5 patients in the present series, a gross or microscopic cause for ileocecal perforation is not evident. Thelander reported a similar experience. Although his series included cases in which pneumoperitoneum had not been demonstrated roentgenologically, he noted a striking predilection for involvement of the terminal ileum.

Infection as an important factor in such perforations was suggested by Thelander, Walters and Chaffin, and Hubbard and King. Although Thelander noted a lack of inflammatory response as found pathologically in perforations of the terminal ileum, he and others described inflammation of Peyer's patches such as are found in typhoid fever. Van Ulrich and associates described such perforations occurring during epidemics of ulcerative enteritis in premature infants. Nevertheless, convincing proof of a cause and effect relationship between infection and ileocecal perforations is lacking. One child in our series was found at operation to have pneumatosis cystoides intestinalis and pneumoperitoneum, presumably from the escape of air through the involved intestinal wall. This entity is a not uncommon autopsy finding in infants dying from severe diarrhea and accounts for a number of cases of pneumoperitoneum discovered for the first time at autopsy.

The prognosis for infants suffering from pneumoperitoneum remains dismally poor. One survivor was reported in Thelander's 85 patients, 13 of whom were subjected to operation. Although attempts at surgical repair are often undertaken in infants who are moribund from advanced and unrecognized peritonitis, the increasing numbers of survivors being reported by such workers as Linkner and Benson, Bird and associates, Beatty and Bohn, Walters and Chaffin, Schiff, Daniel and associates, and Miller reflect improved diagnostic awareness and prompt surgical intervention. Unfortunately, the limited opportunities for pathologic study in surviving patients render difficult conclusions as to the pathogenesis of those perforations compatible with life.

SUMMARY

1. Experience with 15 consecutive infants with pneumoperitoneum undergoing laparotomy at the Cook County Children's Hospital is presented.

2. The varied etiology, diverse sites of perforation, and diagnostic techniques of value in the detection of pneumoperitoneum are emphasized.

3. Surgical management of the responsible disease based upon preoperative and operative study is outlined in an effort to formulate an over-all approach to this problem.

4. Early recognition of pneumoperitoneum by the pediatrician, intelligent roentgenologic investigation, and prompt surgical intervention are essential if survival is to become the rule rather than the exception in these infants.

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MODIFIED MASTECTOMY FOR OLDER, POOR RISK PATIENTS

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STAFF MEMBERS at our institution have long believed that a true radical mastectomy is the proper basic treatment for breast cancer, adding chest wall dissection in suitable patients. In younger women this complete operation has no greater mortality or morbidity than less complete forms of treatment. When one deals with women of 70 or older, however, the extent of the operation, the amount of tissue removed, the time under anesthesia all become problems to consider. We have analyzed our long term experience to determine what the risks are of radical mastectomy, on the one hand, and less extensive operations which may remove less tumor as well as less tissue, on the other.

MATERIAL

The original comparisons were made among 1,441 women treated during the years between 1940 and 1943. The total number of 95 women 70 years old or older was not enough in some instances; important differences were suggested that proved not to be statistically significant. Hence the series of women over 70 years old was expanded to cover the years between 1944 and 1947 as well. This permitted another 147 older patients to be considered.

In this group of 242 women, 94 had been treated by modified operations, whereas 148 had had standard radical mastectomies. Twenty-four patients had simple mastectomies in which none of the axillary contents were removed since no nodes were palpable. Thirty-one patients had simple mastectomies plus low axillary dissections because 1 or 2 nodes were palpated low in the axilla. Thirty-nine patients had simple mastectomies plus removal of about two-thirds of the axillary contents. Multiple nodes were palpable in the axillary component of the specimens.

The first procedure was to test the later group against the earlier to see if it was legitimate to consider them together. In all measured characteristics: size of tumor, histologic type, node metastases, and fate after treatment, the 1944 to 1947 group resembled the earlier one; no reason for not merging them could be found. Neither were there significant differences between cancers removed radically and those taken off by modified operations as to size or cell type. The medical evaluation of the patient seemed to have been the only basis for the decision to do a modified operation.

RESULTS

It first must be noted that breast cancer in older women is not quite typical.

As shown previously by Robbins and associates, old women tend to delay seeking treatment for breast cancer (Fig. 1). Only about half as many came for treatment within the first 2 months after discovery of the lesion. Even this figure seems exaggerated since some of the short histories reflected complete senile unawareness of tumor until or even after ulceration.

As expected, the longer delays before treatment led to the finding that breast tumors were significantly larger in the older women. Sixty-three per cent of the older group compared with 53 per cent of the younger, or a fifth more, had cancers larger than 3 centimeters in diameter.

At the same time it was noted that significantly more of the cancers in older women were of the histologic types and grades associated with better than average prog-

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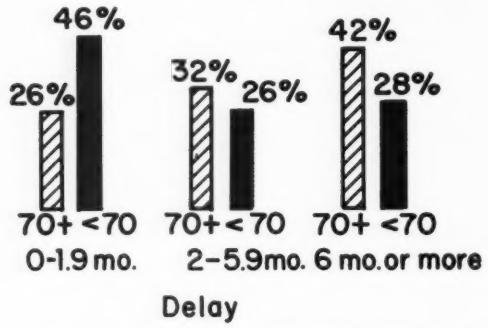

FIG. 1. Relation between patient age and interval between onset of symptoms and treatment.

nosis: medullary, colloid, papillary, comedo cancers, grades I and II duct cancers, and the type of grade III duct cancer with peripheral inflammation (1). There was a relative deficit of anaplastic duct cancers and lobular cancers, which have the same prognosis as the anaplastic duct type. The cancers in 53 per cent of older patients were low grade compared with 38 per cent in the younger group.

As a result of the balancing of the two factors, larger lesions but lower grade ones, there was not the increase in axillary metastases usually associated with increased patient delay. Actually, there was a slightly lower incidence of positive nodes in women over 70, though the difference is not statistically significant, namely, 55 per cent as compared with 60 per cent.

This finding has an important bearing on the question of modified operations. The argument against incomplete axillary dissection is that it may leave excisable tumor behind. How many women were exposed to this risk is indicated by the number who had demonstrable metastases among the group in which the axilla was examined. If long delays meant many more patients with positive axillary nodes, there would be a strong a priori argument against leaving the upper part of the axilla. Our figures indicate no such increase in axillary involvement and, in fact, as delay decreases with education, older women should have a lower than average rate of nodal metastases.

INCREASED RISK

Radical mastectomy. During the period in question, radical mastectomy carried a definitely increased operative mortality. Five of 148 or 3.4 per cent of the patients treated by radical operation are listed as operative deaths. This is about 10 times the rate seen in younger women treated in the years between 1940 and 1943, among whom there were 6 operative deaths in 1,346 patients or 0.4 per cent. The current figure is 0.35 per cent.

This risk was abolished in our group by recourse to modified operations. Despite the fact that these operations were utilized because the patients were poorer operative risks, no deaths occurred in 94 operations.

The problem thus seems to be to determine whether or not this gain in patient salvage is counterbalanced by increased cancer deaths among the conservatively treated patients.

Modified operations. Figure 2 gives the absolute survival rates for the three groups: younger women treated by radical mastectomy, older women treated by radical mastectomy, and older women treated by modified operations. At 5 years the difference lies between the older and younger women with no deficit attributable to the modified group. At 10 years a difference does appear; only 4

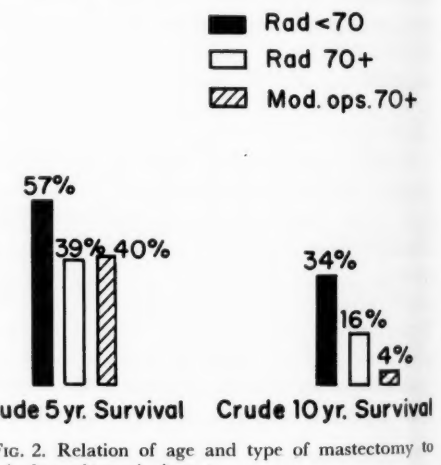

FIG. 2. Relation of age and type of mastectomy to survival; crude survival rates.

per cent of the modified group were alive as opposed to 16 per cent of the radically treated older group.

Two explanations, of course, are possible. The difference may be due to an excess of cancer deaths in the modified group or to an excess of deaths from unrelated diseases of old age. The latter explanation seems more likely for the difference in survival of the two radically treated groups.

There is little need for speculation, however, since construction of actuarial tables for cancer automatically corrects for deaths from other causes at the time they occur (Fig. 3). When deaths from other causes are eliminated, the survival rates for women over and under 70 years treated by radical mastectomy are identical.

The second thing that the actuarial curves show is that, up to 7 years, there is no appreciable difference in the cancer mortality of women with modified operations. Between the second and sixth years they actually do a little better than expected. It is only in the later years that a drop is noted.

The significance of this difference should not be overestimated. It was produced by exactly 2 patients of the original 94 dying of breast cancer after deaths from this cause had ceased in the older radical operation group. At the same time, there were twice as many patients alive in the radical operation group, and they lived long enough to have 3 times the years at risk without a further cancer death.

Further argument for considering this small increased risk authentic comes from the fact that it occurs just where it should. The only patients prejudiced by incomplete axillary dissection are those whose cancer has spread to the upper part of the axilla but no further. If the disease is already disseminated, leaving a gram or two more behind should make no difference. Cancer deaths among patients treated by radical operation must represent such prior dissemination. Any excess of deaths because of incomplete operation must by definition result from dissemination beyond the axilla after the time of

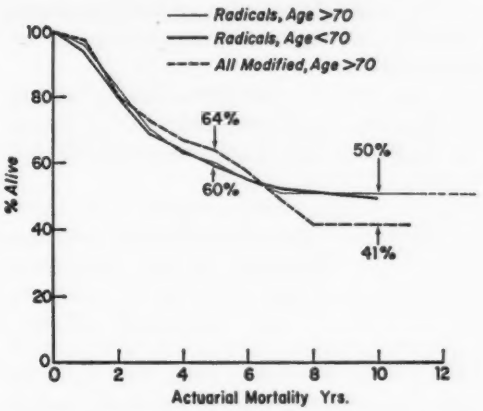

FIG. 3. Relation of age and type of mastectomy to survival; mortality from breast cancer alone.

operation. Such late dissemination should mean late death, cancer deaths added on at the end of the usual death curve for failures of radical mastectomy. This is exactly where the 2 extra deaths in this series occurred.

COMMENT

Assuming for purposes of argument that the small difference between radically and conservatively treated women is real, what does it mean practically? The first point is that while our patients considered poor operative risks had the same absolute 5 year survival rate as did the rest of the women in their age group, few survived much longer than 5 years. The last one of the 94 was lost to follow up at 11 years and presumed dead. Hence only a small residual of these poorer operative risks are exposed to the excess risks of modified operation. Thus, there is only a small delayed risk to a fraction of the original group to be balanced against the immediate and presumably, by medical evaluation, higher risk of the standard operation. If one can legitimately consider years free of disease, it would appear especially clear that, in these older women, modified operations mean an occasional shortening of life by a year or two in return for the much longer period that would be lost by an operative death.

This justification of modified operations does not apply also to younger women for four reasons.

1. In healthy younger women, radical mastectomy carries very little risk; in them, modified operation carries no particular advantage of safety.

2. In younger women, significantly more cancers are of aggressive types that metastasize early and kill more rapidly; inadequate treatment therefore carries a higher price tag.

3. Younger women live far longer if cured; many more enter the period of increased risk, and many more patient years will be lost if patients succumb to the risk because of incomplete operation.

4. There can be definite and demonstrable salvage of patients whose metastases in the apex of the axilla are removed, and, as we hope to show in a subsequent article, most of these long term survivors legitimately can be considered cures.

For all of these reasons, we conclude that if a woman clearly is able to undergo a radical mastectomy, it is the procedure of choice. However, if, and only if, she is a poor operative risk, there seems more to be gained than lost by an incomplete, less extensive procedure.

SUMMARY

About 40 per cent of 242 women over 70 with operable breast cancer were considered poor risks and so were treated by modified operations rather than by radical mastectomy. The operative mortality was thereby reduced; the increased loss from cancer was minimal and appeared in this older group only after 5 years.

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REBOUND REGRESSION IN ADVANCED MAMMARY CARCINOMA

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IT HAS BEEN KNOWN for many years that endocrine manipulation may have a beneficial effect on the course of metastatic mammary carcinoma. This effect was described by Beatson in 1896 who noted regression in the metastatic deposits of mammary carcinoma after removal of the ovaries. Endocrine manipulation may take two forms: additive hormonal therapy with androgens, estrogens, corticosteroids, and progestins or ablative endocrine therapy by surgical removal of the ovaries, adrenals, and hypophysis individually or in combination. Sometimes castration is accomplished by radiation rather than by surgery. All these procedures have shown benefit in a limited number of cases. Apparently, changing the hormonal milieu of the growing cancerous tissue places it in an adverse environment and its growth potential is suppressed. When a patient is receiving additive therapy, cessation of that therapy itself causes a change in the hormonal environment of the tumor. The result may be what is called rebound regression or hormone withdrawal effect and is here defined as the objective improvement seen in advanced mammary carcinoma which follows the cessation of additive hormonal therapy.

Although this phenomenon has been previously recognized, its incidence is not well established. The few articles which mention its occurrence are quite vague. Escher was apparently the first to recognize the phenomenon of rebound regression. He reported its occurrence in 7 of 11 patients who previously had a beneficial response to androgen therapy. Lewison, in his review of 133 advanced cases of the disease treated with sex hormones, indicated that rebound regression can occur in those patients who initially respond or fail to respond to therapy, but no figures were given. Huseby reported on 100 patients treated with estrogens and stated that 9 of 14 patients who initially responded to estrogens subsequently responded to their cessation. He did not indicate what happened to those patients who failed to respond initially to estrogen therapy. Douglas defined withdrawal response as "no response was noted during the administration of the hormone, but a beneficial effect was produced after the drug had been stopped." However, it was not clear whether the beneficial effect was objective or subjective nor was its duration reported. Douglas reported the occurrence of withdrawal response in 9 of 392 estrogen-treated patients and 1 of 30 androgen-treated patients. Baker and associates stated "in about 10 per cent of patients who have received objective benefit to the administration of estrogen, withdrawal of estrogens after relapse will produce an additional short-lived response." There is no further clarification of this statement. Recently, 944 sex hormone-treated breast cancer patients from many collaborating institutions were reviewed (2). The summation of rebound regression is herein quoted, "also worthy of mention was the observation of renewed remission in an occasional patient after withdrawal of the hormonal substance which had induced the initial period of regression. Such examples of a 'therapeutic' effect by omission of therapy are unusual, and the duration of the favorable response ordinarily is brief."

This study was undertaken to try to

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TABLE I.—TOTAL EXPERIENCE EVALUATED

Hormone	*No. of cases*	*No. of trials*	*No. of eval. trials*	*No. of rebound regr.*
Androgen..	605	738	371	13 (M-3)
Estrogen...	342	408	233	21 (M-3)
Corticoid...	117	121	28	0
Progestin...	67	71	42	0
Total....	800	1338	674	34 (M-6)

TABLE II.—DURATION OF HORMONE

	Months			
Hormone	*0–3*	*4–6*	*7–12*	*+12**
Androgen				
Failure...	2	3	2	0
Success...	0	1	0	4
Estrogen				
Failure...	2	3	1	1
Success...	0	1	2	9
Total.....	4	8	5	17*

*Includes 3 patients whose response to additive hormone therapy could not be evaluated.

ascertain the incidence of rebound regressions, to describe under what conditions they occur, and to determine the duration and effect on prognosis of the disease. Certain theoretic and practical implications of these data will also be discussed.

METHOD

The charts of 800 deceased patients who had been seen in the Hormone Therapy Clinic of Memorial Hospital or were private patients were reviewed. All patients had been regularly seen during the course of their illness by either or both of us. Roentgenograms were re-reviewed in all cases in which this technique of study was necessary to evaluate the rebound regression. Measurements taken of the local lesions and certain blood studies were also considered in the total evaluation of the rebound regression.

CRITERIA OF REBOUND REGRESSION

The criteria were essentially the same as those used for regression in additive or ablative hormonal manipulation with 1 exception. For the purpose of this article, the mixed as well as pure rebound regressions are included. These are the cases in which some lesions regress while at the same time new lesions appear or old lesions progress. The only acceptable criterion for any rebound regression is objective evidence of tumor regression. Patients whose disease remained unchanged after cessation of therapy in a previously progressive tumor process are not included. Subjective criteria alone, such as increase in well-being, weight gain, and improved ambulation, are not considered. Return to normal of hormonally induced hypercalcemia is not included unless there is other evidence of regression, either as recalcification of lytic osseous lesions or decrease in size of soft tissue lesions.

RESULTS

A review of the complete experience is presented in Table I. Eight hundred patients received 1,338 additive hormone trials of the listed types. Only 674 additive trials were available for adequate review of the incidence of rebound regression. Of the 674 additive trials evaluated, 34 were followed by rebound responses. The exclusion of cases falls in three general categories.

1. Two hundred and forty-five patients died either during therapy or within 2 weeks of its cessation. The highest incidence in this category of exclusion was in the group of patients who received corticosteroid therapy as a preterminal palliative therapy.

2. This group includes 86 cases in which the patients were menstruating at onset of therapy. Since at cessation of therapy, estrogen function may then become evident again the effect is probably substitution of one form of additive hormone for that of another. This reaction applied to 84 androgen and 2 progestin treated patients.

3. Three hundred thirty-three cases were excluded for a variety of reasons. In some the trials were unsuitable for rebound regression evaluation because of inadequacy of duration of initial hormone course; in others, new therapy was started less than 1 month after cessation of the previous additive therapy without convincing evidence of interim progression of disease; still other patients were inadequately followed up at time of cessation of therapy or at a later date

(the minority); and lastly, there were patients who were not seen again but are known to have died many months later. In a few cases, additive hormone therapy was stopped during remission because of side effects and these cases are excluded.

Table I also illustrates that no rebounds were seen in the small series of corticosteroid or progestin therapy cases.

In Table II is presented the duration of the course of additive hormone therapy after which rebound regression occurred. It also includes whether or not the patient was a treatment success or failure. Twenty-two of 34 patients were given therapy for more than 6 months, 15 of these showing a good response to additive therapy. Twelve of 34 received therapy for 6 months or less; 10 of these were failures. The period of therapy is obviously longer in those who responded well to therapy.

The incidence of rebound regression after an initial beneficial response to the additive therapy and then relapse during therapy was as follows: In 39 trials there were 12 rebounds or 30.8 per cent after estrogen withdrawal, of which 2 were of the mixed type; excluding the latter we find a 25.8 per cent incidence for pure rebound regression after estrogen success. There were 5 rebounds or 10.2 per cent in 49 trials with androgen additive. All rebound regressions after androgen success were pure.

Rebound regressions do occur after failure to the additive sex hormones but are uncommon. Three of the 7 rebound regressions —2.2 per cent of 322 trials—after androgen failure were of the mixed type; the pure regression incidence then drops to 1.2 per cent. There were 7 rebound regressions, or 3.6 per cent of 194 trials, after estrogen failure. With the omission of 1 mixed response after failure to estrogen therapy, the adjusted rate for pure rebound regression is 3.1 per cent.

Thus the total experience regardless of success or failure to the previous additive hormone was: 13 rebounds, or 3.5 per cent of 371 trials, after androgen therapy and 21 rebounds, 9 per cent of 233 trials, after estrogen therapy. The adjusted incidence after omission of the 3 mixed responses in the androgen treated cases is 10 in 371 or 2.7 per cent; for estrogens, after omission of 3 mixed responses, the adjusted incidence is 18 in 233 trials or 7.7 per cent.

TABLE III.—DURATION OF REBOUND REGRESSION

Hormone	No. of trials	Months		
		Mean	Median	Range
Androgen.....	10	10.7	6.0	2–36
Estrogen.....	18	9.2	7.0	4–24
Total.....	28*	9.7	6.5	2–36

*Excludes 6 patients with mixed response.

TABLE IV.—SURVIVAL TIME FROM ONSET REBOUND REGRESSION

Hormone	No. of cases	Months		
		Mean	Median	Range
Androgen....	12	25.9	18.0	4.5–75
Estrogen.....	19	25.0	19.0	6–82
Total.....	31*	25.4	19.0	4.5–82

*Three responses excluded from data.

Duration of the rebound regression is shown in Table III. The duration of response is calculated from the cessation of the therapy until the first evidence of progression of the disease. There is a time lag between the start of additive hormone and the appearance of objective improvement. A comparable time must elapse between the cessation of additive therapy until objective improvement can be observed. For example, local lesions may show evidence of regression as soon as 2 weeks after cessation of therapy. Pulmonary and pleural lesions may show roentgenographic evidence of regression as soon as 1 month after the cessation of the therapy. Osseous lesions may take months before being noted on roentgenologic study; however, the alkaline phosphatase flare seen in patients receiving additive therapy at 2 to 3 weeks has also been observed at 2 to 3 weeks after cessation of therapy and may presage subsequent favorable changes in the roentgenograms. The duration of the rebound covers a wide range; however, the average duration is similar to that manifested by additive hormone responders. In regard to those patients who initially showed

response to additive therapy the rebound regressions were longer than the initial response in 6 cases, shorter in 7 cases, and about equal in 2 cases. These data show that the rebound regression is fully as substantial as the response to additive hormones.

Table IV presents survival time from cessation of additive therapy in the rebound regressers. The range is variable but the means for androgen and estrogen are quite close. Since only 3 patients were those with purely local disease, one can see that the prognosis is quite good and the survival time prolonged in those patients who experience a withdrawal effect. It is at least equal if not better than the expected survival time in additive hormone responders as reported in a recent article (2). Three responses were excluded from the data. One patient was observed in rebound regression whose survival time is not known because of lack of subsequent follow up. In 2 patients, each of whom experienced 2 rebound regressions, survival data were calculated only from onset of the first rebound regression.

DISCUSSION

At the onset it must be stated that rebound regression will not be recognized unless one specifically looks for it after the cessation of each course of additive hormone therapy. This means that baseline studies, such as measurements, photographs, skeletal survey, roentgenograms of the chest, and laboratory tests must be made at the cessation of therapy so that any changes which occur later can be well documented as due to hormonal withdrawal. The patient's condition should be evaluated with proper studies after exactly as before treatment.

The phenomenon of rebound regression has three important aspects for those clinicians who treat metastatic mammary carcinoma. The first is in palliation of the disease, the second is in drug evaluation, and the third is in the theoretic implications of the phenomenon.

In regard to palliation, the figures on duration of rebound regression and survival are equal to those obtained in the beneficial responses seen with additive hormone therapy. Rebound regression should therefore be considered as a therapy unto itself and, unless there is definite progression of disease on cessation of the hormone, no further therapy is indicated. If further therapy is given before this phenomenon has the chance to occur its effect may be negated. We have seen a patient in dire straits from cerebral metastases with papilledema, hypercalcemia, headaches, and extreme visual loss respond to the cessation of androgens with subsidence of all these physical and subjective complaints. The patient was saved, at least temporarily, from the rigors of what would have been radiation therapy to the cranium.

In the sphere of drug evaluation, it is not difficult to see that if new therapy is started soon after cessation of additive hormone therapy and a beneficial response is obtained, its causation will be unclear. This observation applies to subsequent hormonal or nonhormonal chemotherapy. Because rebound regression is not very frequent, one may believe that this phenomenon is not important. However, if at the start of trials of a new agent which turns out eventually to be worthless a rebound regression occurs early in its testing and is unrecognized, one would be forced to extend further observations on this agent which might be detrimental to patients and a waste of patient material and physician effort. Therefore, one should have convincing evidence of progression of disease after cessation of hormone therapy before instituting treatment with either standard or experimental chemotherapy.

The final importance of rebound regression lies in its theoretic significance. One can of course plead ignorance, and probably should, about the mechanism of beneficial response to additive hormones in patients with metastatic mammary carcinoma. The usual explanations for these responses, and the simplest, are that the additive hormone

changes a favorable internal milieu to one unfavorable for tumor growth or alternatively that the hormones have a direct antitumor action. These explanations apply to all hormones. It has also been postulated for androgens and progestins that they are acting as antiestrogens at the end organ, whereas, in the case of the corticoids, it has been suggested that they act as a suppressant of adrenal production of estrogen. Additive hormones have also been said to manifest their favorable effect by pituitary suppression.

Estrogens, in particular, are believed to exert their beneficial effect by pituitary suppression or direct antitumor action. However, it is difficult to accept rebound regression as being due to the release of pituitary inhibition.

The observation of unpredictable variations in the response of tumors to additive sex hormone therapy—regression during therapy, progression during therapy, obvious exacerbation during therapy, rebound regressions after both favorable and unfavorable response to therapy, lack of rebound regressions and mixed responses both during and after therapy—has led us to conceive the following hypothesis: a given tumor may be heterogeneous in its capacity to react to hormonal manipulation. It might consist in varying proportions of at least three different cell populations: hormone sensitive, i.e., those tumor cells which suffer adverse effect in the presence of the hormone; hormone dependent, i.e., those tumor cells whose growth is promoted in the presence of the hormone; hormone independent, i.e., those tumor cells which are unaffected by the hormone.

The response to additive therapy depends on which cell population is causing progression of the disease at the time therapy is started. Thus, regression of lesions would suggest a predominantly hormone sensitive cell population; progression of the disease might indicate a predominantly hormone independent population; and obvious exacerbation would suggest a predominantly hormone dependent cell population. The mixed response during therapy represents improvement in some lesions, progression in others or the appearance of new lesions which would occur in a tumor composed of significant numbers of both hormone sensitive and hormone independent cells.

In the case of rebound regressions which, of course, occur on hormone withdrawal, we postulate that the lesions are composed chiefly of hormone dependent cells which would be expected to regress in the absence of the hormone. In a sense this is medical ablation. An interesting observation in the course of this study was that rebound regressions occurred only after the use of androgens and estrogens which are known to have the capacity to stimulate human breast cancer. No rebound regressions were seen after corticoid and progestin therapy, neither one of which seems to have the inherent ability to stimulate these tumors.

When rebound regression occurs after a favorable response to hormone therapy, the explanation would be as follows: the great majority of the population of tumor cells which were causing progression of the disease were hormone sensitive. The therapy brought about almost complete destruction of those cells, which registers to our gross clinical evaluation as "regression." However, there may be some hormone dependent cells which have continued to grow but which constituted such a minority as not to interfere with the beneficial response. Eventually the relapse on therapy was due to the overgrowth of these hormone dependent cells, which now have become the majority of the total tumor present. Cessation of the therapy by removing the stimulus from the hormone dependent cells at this point will result in the rebound regression. When rebound regression does not occur it is probably because the overgrowth of cells causing progression of disease consisted of hormone independent cells.

When rebound regression occurs after unfavorable response to hormone therapy the following explanation would apply: At

the start of therapy the predominant cell population was hormone dependent. The addition of the hormone facilitated further growth of the tumor. At the cessation of therapy these hormone dependent cells would regress. As has been noted before, those of our patients who had rebound regressions after failure of hormone therapy were not improved over their pretreatment state, and for this reason, it is pointless to attempt to exacerbate a tumor by hormone therapy in order to capitalize on a possible rebound regression. Furthermore, the incidence in our series of rebound regression after failure to respond to hormone is too low to warrant such an approach.

The lack of occurrence of rebound regression after failure to hormone therapy would indicate that the tumor failed to respond originally because it was composed of predominantly hormone independent cells.

For the mixed response which occurs as a rebound phenomenon we postulate that the progression of tumor which led to cessation of therapy was due to significant numbers of both hormone dependent and hormone independent cells. The hormone dependent cells regress and the hormone independent cells continue to progress.

Although for the purposes of this article the hypothesis that breast carcinoma may have heterogeneous cell population has been used only to explain variations in response to additive hormone therapy, the theory might help to clarify some of the more poorly understood variations in response to sequential endocrine manipulations. For example, in the patient whose tumor has not responded to adrenalectomy after a castration remission, the explanation in terms of our theory would be that at the time of castration the tumor was mostly composed of hormone dependent cells which regressed when deprived of estrogen; subsequently, the minority of hormone independent cells grew into predominance and further deprivation of estrogens by adrenalectomy was ineffectual.

SUMMARY

1. Six hundred seventy-four trials of additive hormone therapy in female metastatic mammary carcinoma have been reviewed for the incidence of rebound regression.

2. The incidence of this phenomenon was 3.5 per cent after androgens and 9.0 per cent after estrogens. The phenomenon did not occur after corticoid or progestin therapy.

3. The circumstances of the occurrence, duration, and effect on prognosis of rebound regression have been analyzed.

4. The practical theoretic implications of this phenomenon are discussed.

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MEASUREMENT OF BLOOD FLOW IN HUMAN LOWER EXTREMITY BY INDICATOR-DILUTION METHOD

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FOR THE MOST PART, only relative determinations of the arterial supply to human limbs have been available, except for plethysmography and flowmeter determinations. Plethysmography is of questionable accuracy because of individual variations in the compressibility of the deep venous outflow, and the use of flowmeters, with the exception of methods under development which use miniature probes, requires the surgical exposure of the artery.

It is surprising that the indicator-dilution principle has not heretofore been applied to human limbs, except for the study by Andres and associates of flow from the muscles of the forearm. The single artery, basic to the method, exists in the lower extremity, except when severe occlusion at more proximal levels has caused an enlargement of collateral flow; in these cases the collaterals rarely re-enter the main channel for distribution.

Almost invariably the common femoral vein is available as the total outflow for the lower limb, with mixing of blood from superficial and deep parts. Rarely, the obturator or gluteal veins may take over the mixed venous drainage. Sometimes the vein remains occluded by previous phlebitic processes and is not available.

One disadvantage of measuring total limb flow is that one cannot distinguish variations in flow in different parts of the limb, such as may occur with local arterial occlusion or conversely by open arteriovenous shunts.

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METHOD

We have used radioiodinated (I^{131}) human serum albumin (RISA), in doses of about 25 microcuries, as the tracer substance, injected as a bolus into the common femoral or terminal external iliac artery. The examination is carried out in a room of comfortable temperature, controlled by air conditioning. The subject is not fasting. He lies supine, and the leg is adjusted so that the tibia and femur are on a level line. The injection is made upstream, as rapidly as possible, through an 18 gauge indwelling Cournand needle and, since the flow is fairly high, adequate mixing could be expected. Experience with arteriography would seem to confirm this view. The outflow in the companion vein is sampled through an indwelling 16 gauge needle, the blood being conducted through a short piece of wide vinyl tubing, to lower resistance of venous flow, to test tubes rotated past the tubing by a fractionator. Blood collection in 5 second samples during a 90 second period after the arterial injection was found adequate. Sampling for 2½ minutes was found to offer no advantage over the shorter period.

The amount of blood in each tube, collected from different subjects, varied from .3 to 1.5 milliliters. The activity in pipetted aliquots of the blood samples is determined in a scintillation well counter, and the net counts per minute for each aliquot are plotted against time on linear paper. The activity of the venous blood rises to a sharp peak at 15 to 50 seconds, an average of 36.5 seconds, which is delayed in the presence of arterial diseases. The decline of this pri-

TABLE I.—REPRODUCIBILITY OF THE METHOD

	Total limb flow, ml. per min.	
	Patient 18	*Patient 29*
Before lumbar sympathectomy		
Experiment 1	209	316
Experiment 2	220	338
After lumbar sympathectomy		
Experiment 1	361	507
Experiment 2	365	490

TABLE II.—TOTAL BLOOD FLOW IN THE LOWER EXTREMITY IN NORMAL, HYPERTENSIVE, AND VASOSPASTIC SUBJECTS

Patient No.	*Age, yrs. Sex*	*Total flow, ml./min.*	*Total flow per 100 ml. limb*
NORMAL SUBJECTS			
1	23 M	886	7.78
2	82 M	672	7.50
3	81 M	681	7.39
4	85 M	660	7.13
5	84 M	660	7.06
6	21 M	694	7.01
7	49 M	588	6.92
8	19 M	519	6.43
9	81 M	508	6.39
10	80 M	655	6.35
11	45 M	648	6.30
12	43 F	450	6.30
SUBJECTS WITH HYPERTENSION OR PERIPHERAL VASOSPASM			
13	48 M	546	5.77
14	33 M	480	5.73
15	46 F	566	5.46
16	51 M	447	5.38

mary circulation is extrapolated to zero by using the data from a semilogarithmic graph where counts per minute are plotted against time. The downslope of the curve on the semilogarithmic paper is a straight line and the beginning of the recirculation is detected as a break from the exponential decline (Fig. 1). The time required for recirculation is long for the lower limb, ranging from 45 to 80 seconds, an average of 61.2 seconds, and it is delayed in the presence of arteriosclerosis of the limb or in patients with low cardiac output.

This time is confirmed by the observation of events during the additional measurement of cardiac output mentioned later: the time from the injection of RISA in the femoral vein and the peak of concentration in the femoral artery in 12 older patients ranged between 20 and 32.5 seconds with an average of 26.8 seconds. When this latter result is added to the average time of the appearance of the primary peak in the venous sampling—36.5 seconds—an average of 63.3 seconds is obtained for the recirculation time which is approximately the same as that observed in the semilogarithmic graph—61.2 seconds.

Computation of total flow in the limb was made according to the formula given by Kinsman, Moore, and Hamilton:

$F = \frac{I}{C_{av}t}$, where F = blood flow in the limb in milliliters per minute, I = total injectate in counts per minute, C_{av} = average concentration of radioactivity in the venous blood during the primary circulation in counts per minute, t = duration in minutes of the primary circulation, $C_{av}t$ = area by planimetry under curve of primary circulation, counts per minute per milliliter × minutes.

The total injectate is determined by repetition of the injection of the same amount of RISA, through the same equipment as used for the arterial injection, into a liter of water and by measurement of the activity of an aliquot of this diluted material equivalent to that taken from the blood samples.

The reproducibility of the method was established by repetition of the procedure after allowing 10 minutes for establishment of equilibrium of radioactivity in the blood stream, and using about twice the amount of RISA as in the first determination (Table I).

Since limbs vary in size, it appeared desirable to relate the flow rate to limb volume. The volume was determined by causing the patient to stand with the limb in a tank. The tank has an adjustable bottom, so that its upper limit was always at the level of the groin. The tank was filled with

small plastic pellets, the limb was withdrawn, and the volume was determined by the measured quantity of pellets required to bring the content to the top again. Limb volume was found to vary from 6,100 to 11,380 milliliters. Blood flow could now be expressed in milliliters per minute per 100 milliliters of limb.

Two other relationships also made were: total limb flow as a percentage of total body blood volume, and total limb flow as a percentage of cardiac output. The blood volume is easily determined by comparing the radioactivity of a sample of venous blood, after equilibrium is established, with the total injectate. Cardiac output was determined after an injection of RISA into the femoral vein, with collection of 2.5 second blood samples from the companion artery, with calculation of flow in the same manner as flow through the limb.

We have also begun to calculate the "vascular space" in the limb, according to the principle of Stewart and Hamilton that the volume of the system between the injection and sampling sites is equal to the product of the volume rate of flow and the mean transit time.

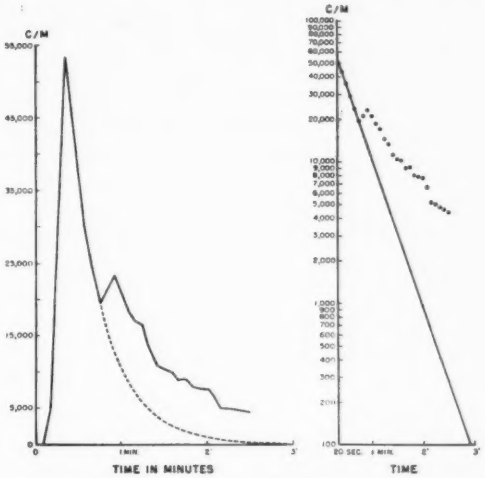

FIG. 1. Blood flow in 22 year old normal male: 694 milliliters per minute or 7.01 milliliters per minute per 100 milliliters of limb. Radioactivity of the femoral venous blood plotted as a function of time after femoral arterial injection: on linear paper, left, and on semilogarithmic paper, right. The extrapolation of the downslope, to delineate the primary circulation curve, is shown as the broken line on the left and the straight line on the right.

RESULTS

Measurement of the blood flow in the limb has been carried out in 36 subjects, with a total of 51 curves, which included repetition after various maneuvers. Data from 3 additional subjects were discarded, in 2 because of departure of the curves from the usual form and in a third because of apparent extravasation of the injectate.

Table II is a summary of our results in 12 normal subjects, and 4 affected by hypertension (Patients 13 and 16) or chronic peripheral vasospasm (Patients 14 and 15). The total limb flow in the normal subjects ranged from 450 to 886 milliliters per minute (average 635) or 6.30 to 7.78 milliliters per minute per cent of limb volume (average 6.88). In the second group, the total flow was from 447 to 566 milliliters per minute (average 510) or 5.38 to 5.77 milliliters per minute per cent of limb volume (average 5.58). This considerable decrease is probably due to the severe suppression of flow effected by an increased peripheral resistance, recently also demonstrated by Cannon and associates utilizing the electromagnetic flowmeter.

Flow was determined in 18 patients with peripheral arteriosclerosis. They are divided according to the level of major obstruction (Table III). Total flow for all groups ranged from 143 to 669 milliliters per minute (average 362) or 2.24 to 5.72 milliliters per minute per cent of limb volume (average 4.50). Generally, the higher the obstruction, the more restricted is the flow, but this rule is overcome by individual differences in the diffuseness of the disease.

The study also included 1 patient with scleroderma (Patient 35 in Table IV); and 1 with myxedema, whose total flow was 255 milliliters per minute or 3.40 milliliters per minute per cent of limb volume.

TABLE III.—TOTAL BLOOD FLOW IN THE LOWER EXTREMITY IN ARTERIOSCLEROTIC OCCLUSION AT VARIOUS LEVELS

Patient No.	*Age, yrs. Sex*	*Total flow, ml./min.*	*Total flow per 100 ml. limb*
	PARTIAL AORTOILIAC		
17	51 M	373	4.28
18*	64 F	214	3.50
	FEMOROPOPLITEAL		
19	66 F	409	4.79
20	77 M	394	4.74
21	76 M	423	4.71
22	68 M	429	4.21
23	61 M	361	3.84
24	58 F	324	3.51
25	81 F	204	3.18
26	63 F	143	2.24
	BELOW POPLITEAL		
27	49 M	669	5.72
28	70 F	403	5.55
29*	56 M	327	5.40
30	80 M	417	5.37
31	83 M	362	5.00
32	89 M	320	4.85
33	68 F	407	4.70
34	82 M	339	4.56

*Average values from Table I.

Total limb flow relative to total blood volume ranged from 8.91 to 15.11 per cent of the blood volume (average 12.90) in the normal subjects; 7.27 to 12.68 per cent (average 9.79) in the hypertensive and vasospastic patients. Among the arteriosclerotic patients, the values were 5.17 to 6.02 per cent (average 5.59) in partial aortoiliac occlusion; 5.00 to 9.87 per cent (average 7.66) in femoropopliteal obstruction; and 6.02 to 9.27 per cent (average 7.75) with obstruction below the popliteal artery.

The total limb flow in 6 normal octogenarians constituted 13.5 to 18.0 per cent (average 15.9) of the cardiac output, which ranged from 3,191 to 4,965 milliliters per minute (average 4,058). In 4 elderly arteriosclerotic patients, the limb flow was 3.4 to 13.3 per cent (average 8.9) of the cardiac output, which ranged from 3,121 to 4,146 milliliters per minute (average 3,673).

TABLE IV.—EFFECT OF VASODILATING PROCEDURES ON TOTAL LIMB FLOW

Patient No.	*Condition*	*Total flow, ml./min.* B	A	+%	*Total flow per 100 ml. limb* B	A
	LUMBAR SYMPATHECTOMY					
18	Arteriosc.	214	363	69.6	3.50	5.95
26	Arteriosc.	143	223	55.9	2.24	3.49
22	Arteriosc.	429	665	55.0	4.21	6.53
29	Arteriosc.	327	498	52.2	5.40	8.23
23	Arteriosc.	361	499	38.2	3.84	5.31
35	Scleroderma	268	366	36.5	4.39	6.00
19	Arteriosc.	409	534	30.5	4.79	6.24
	VASODILATOR DRUG*					
14	Vasospasm	480	635	32.2	5.73	7.58
	MUSCULAR EXERCISE					
11	Normal	648	896	38.2	6.30	8.72
15	Vasospasm	566	657	16.0	5.46	6.33
24	Arteriosc.	324	365	12.6	3.51	3.95

B, before and, A, after the procedure.
*Reserpine for 10 days.

TABLE V.—THE 95 PER CENT CONFIDENCE LIMITS ABOUT MEAN VALUES IN NORMAL AND ARTERIOSCLEROTIC PATIENTS

	Normal	*Arteriosclerotic*
Total limb flow, ml. per min.	635±71 (564 to 706)	362±56 (306 to 418)
Total limb flow per 100 ml. limb	6.88±.33 (6.55 to 7.21)	4.45±.45 (4.00 to 4.90)
Total limb flow per cent of blood volume	12.90±1.12 (11.78 to 14.02)	7.61±.80 (6.81 to 8.41)

The influence of vasodilating procedures in a limited number of patients is shown in Table IV. Substantial increases were found after lumbar sympathectomy. The increases with exercise were rather modest, but the exercise was limited by the presence of the arterial and venous needles. In performing the exercise, the patient in supine position thrusts the foot 40 times against a spring loaded lever located above the table, so as to exercise the thigh extensors and calf flexors.

From our data one may make certain statistical observations. The 95 per cent confidence limits for mean values are given in Table V. The observations on cardiac output are too limited for any statistical statement.

We have also calculated the 95 per cent confidence limits for an individual case in the relation between total limb flow and limb volume. The following values were obtained: 6.88 ± 1.14 (5.74 to 8.02) in normal and 4.45 ± 1.92 (2.53 to 6.37) in arteriosclerotic patients. There is therefore a region where the results obtained from normal and arteriosclerotic subjects overlap. If we take a value halfway between the two averages, we obtain 5.67. The probability is that the values will be above 5.67 in about 10 per cent of the arteriosclerotic patients and below 5.67 in 2.5 per cent of the normal patients. This difference is caused by the larger variation in total limb flow among arteriosclerotic patients. If one considers a break off point of 6.00, then there will be about a 6 per cent probability of a value below 6.00 in the normal subject and above this value in the arteriosclerotic patient.

SUMMARY

The indicator-dilution technique was applied to measurement of the blood flow in the human lower extremity. Iodinated human serum albumin was injected into the femoral artery, and blood samples were taken from the accompanying vein. The curve of concentration of radioactivity in these samples plotted as a function of time gave the expected peak and exponential decline essential to the method.

The total blood flow was thus measured in 36 subjects: 12 normal and 24 with functional or organic arterial disease. Some observations were made after vasodilating procedures. Total blood flow was related to limb volume, total body blood volume, and cardiac output.

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PRIMARY RESECTION AND ANASTOMOSIS IN THE TREATMENT OF PERFORATED LESIONS OF THE COLON, WITH ABSCESS OR DIFFUSING PERITONITIS

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IN THE SURGICAL MANAGEMENT of patients with acute perforated lesions of the colon, the generally accepted methods of treatment are: simple drainage, closure and drainage, proximal colostomy, exteriorization, or a combination of such procedures. Primary resection with anastomosis in the presence of either local or free pus is usually considered interdicted.

In this study, a comparison of the results obtained in the treatment of perforated lesions of the colon by primary resection and multiple stage operations is presented.

CLINICAL STUDY

During the 11 year period between 1949 and 1960, 29 patients with perforated lesions of the colon complicated by either local or diffusing peritonitis were treated. In 11, or 37.9 per cent, the cause of the perforation was cancer of the colon, and in the remaining 18 patients, 62.1 per cent, it occurred as a complication of diverticulitis of the sigmoid colon.

In the group of 11 patients with cancer of the colon, 6, or 54.6 per cent, were women and 5, or 45.4 per cent, men. The average age was 63.4 years. The group of 18 patients with diverticulitis of the colon was comprised of 7 women, 38.9 per cent, and 11 men, 61.1 per cent. The average age was 60.9 years. The average age of the patients treated by primary resection was 58.2 years compared with 63.8 years for those patients in whom multistage operations were performed.

The 29 patients were separated into two groups according to the type of surgical treatment prescribed. Group 1 was comprised of 10 patients, 6 with diverticulitis and 4 with cancer of the colon, each of whom was treated by immediate resection and primary anastomosis. There was 1 death.

In the 6 patients with diverticulitis a large abscess, i.e., one containing 150 to 300 cubic centimeters of pus, was present in 4, and in the remaining 2 there was diffusing peritonitis, one of whom had a concomitant cancer of the colon with stenosis immediately distal to the site of a perforated diverticulum. In these 6 patients there were 2 with complications; one had a combined fecal fistula and wound dehiscence and the other a fecal fistula. There were no deaths.

In the 4 patients with cancer of the colon and perforation, a large abscess was present in 3, and in 1 there was diffusing peritonitis concomitant with an occult pelvic abscess, containing 200 cubic centimeters of pus. In 1 of the patients with an abscess, the lesion was in the region of the hepatic flexure and in the remaining 3 patients it was located in the sigmoid colon. In these 4 patients there were 2 with complications; one had a fecal fistula and the other diffusing peritonitis. There was 1 death, the patient with the diffusing peritonitis, who died on the seventh postoperative day. Necropsy showed gross leakage in the center of the anastomosis anteriorly. This leakage was considered an error in technique.

Group 2 was comprised of 19 patients, 12, or 63.1 per cent, with diverticulitis and 7, or 36.9 per cent, with cancer of the colon, each of whom was treated by a multistage operation. In the 12 patients with diverticulitis

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and perforation, an abscess was present in 6, and in the remaining 6 there was diffusing peritonitis. Major postoperative complications occurred in 7, or 58.3 per cent, and there were 4 deaths, 33.3 per cent. In each of the 7 patients with cancer of the colon and perforation, an abscess was present. There was none with diffusing peritonitis. Postoperatively there were 3 major complications, 43.0 per cent, and 3 deaths, 43.0 per cent.

The first stage operation most commonly performed was a transverse colon colostomy either alone or combined with closure of the perforation or else peritoneal drainage. Ileotransverse colostomy and drainage alone were the next in frequency, respectively. After the first stage operation in the 19 patients comprising group 2 there were 10 major complications, 52.6 per cent, and 7 deaths, 36.2 per cent. Upon completion of the multistage procedures there were 39 operations performed upon 19 patients. Of these 19 patients there were major postoperative complications in 15 and 9 died. This is a patient morbidity rate of 78.4 per cent and a patient mortality rate of 47.3 per cent. In the 39 operations performed, the operative morbidity and mortality rates were 38.4 per cent and 23.0 per cent respectively.

COMMENT

In a review of the clinical data presented, the results obtained in the treatment of perforated lesions of the colon by primary resection and anastomosis are significantly better than when multistage operations are employed.

It may be argued that the patients who were treated by primary resection were selective and accordingly better surgical risks. On the contrary, this group included an 82 year old acutely ill woman with both diffusing peritonitis and occult pelvic abscess as complications of a cancer of the sigmoid colon with perforation. When operated upon, the temperature was 102.2 degrees F. and the bowel lumen proximal to the site of perforation and extending to the level of the splenic flexure was filled with feces. A left hemicolectomy with primary end-to-end anastomosis between the left half of the transverse colon and the rectosigmoid was performed. For technical expediency the scope of the operation was extended to include the fecal laden segment which thereby obviated the possibility of spillage of the colon contents into the peritoneal cavity. Subsequent to the anastomosis, palpation of the liver revealed the presence of multiple metastatic foci. The patient was discharged from the hospital on the eleventh postoperative day in satisfactory condition.

In comparison, a 63 year old woman with cancer of the sigmoid colon, perforation, and abscess was treated by drainage of the abscess and the performance of a complementary transverse colon colostomy. Approximately 3 weeks postoperatively, tumor growth within the abdominal wound was observed and proved on biopsy. Similar occurrences have been reported by Donaldson (5) and Ackerman and Wheat. Accordingly, it is believed almost mandatory to perform a primary resection for cancer of the colon with perforation.

The patients in whom primary resections were performed were consecutive and unselected. The acuteness of the emergency would frequently have precluded a "bowel prep," if such were desired. Since 1955, the use of locally acting antibiotics and chemotherapeutic drugs in the preoperative preparation of patients for elective operations upon the colon has been discontinued. Instead, stress has been placed on mechanical cleansing by the use of saline catharsis and soda bicarbonate enemas, morning and evening, for 3 to 4 days before the operation. The results to the present have not warranted a change in this method of preoperative preparation. Postoperatively, parenteral antibiotics and chemotherapeutic drugs are prescribed as may be indicated, but none of the locally acting variety is administered.

The extent of bowel resection varied according to the cause of the perforation. In diverticulitis, the length of colon removed was sufficient to encompass the inflamma-

tory lesion and permit the transection of the bowel through relatively normal tissue. It is neither necessary nor recommended to remove all or as much as possible of the colon inhabited by diverticula. In perforated cancers of the colon, the tumor and its lymphatic drain are resected en bloc provided there are no remote metastases. In 1 patient, the first of the series of primary resections which comprise this study, a large—250 cubic centimeter—abscess was drained and a complementary extended left hemicolectomy with omentumectomy and aortocaval node dissection was performed. The postoperative course was uncomplicated. The patient died of an intercurrent disease 2½ years after operation. Accordingly, in the treatment of cancer of the colon, the concomitant presence of perforation and peritonitis does not of necessity preclude the performance of an adequate operation.

In all colon resections, either elective or emergency, the importance of lack of tension on the suture line, a good blood supply, and a secure anastomosis cannot be overemphasized. To avoid tension on the suture line, mobilization of the splenic flexure may be necessary. In the restoration of bowel continuity, a two layer, open anastomosis, using interrupted sutures of fine, No. 4-0 silk, is performed routinely. Immediately before the anastomosis the transected ends of the bowel and their respective lumens are irrigated with copious quantities of hot (60 to 65 degrees C.) saline solution. This is done both to dilute the toxins locally and to effect a concomitant bactericidal, and where applicable, a possible cancericidal, action. In cases of cancer of the colon, irrigations with anticancer drugs have not been substituted.

Upon completion of the anastomosis, a Penrose drain is usually inserted into either the presacral or the left lumbar gutter. It has its exit through the line of incision rather than through an adjacent stab wound. The closure of the wound in layers with interrupted sutures of Nos. 2-0 and 3-0 silk completes the operation.

If desired, the primary resection of the colon may be converted into a two stage operation by the performance of a complementary proximal colostomy. The indication for colostomy should not be tension on the suture line or a precarious blood supply. If either or both are present, each should be corrected prior to the formation of a colostomy. Otherwise, the minimum of complications cannot be expected. Even though not performed in any of the patients in the present study, primary resection in two stages is particularly indicated when the anastomosis is below the pelvic peritoneal reflection. Under such circumstances, there is a relatively high incidence of postoperative fecal fistulas, the untoward effects of which may be abated by the proximal colostomy.

DISCUSSION

The treatment of perforated lesions of the colon with either local (abscess) or diffusing peritonitis by primary resection is admittedly contrary to the generally accepted surgical principles. Until comparatively recent years the same applied to elective operations on the colon, particularly on the left side. Undoubtedly the exteriorization operation, popularized by von Mikulicz and subsequently modified by Rankin, lowered perceptibly both the operative morbidity and mortality rates. The results obtained by utilizing this method appeared to preclude any possibility of improvement. However, at the present, primary resection with anastomosis is the preferred and the most commonly practiced elective operation for the surgical treatment of cancer of the colon.

It is believed that there should be a reevaluation of our presently accepted methods for the treatment of perforated lesions of the colon. Other than that primary resection is interdicted, there is no unanimity of opinion relative to the specific emergency operation that should be performed. Simple drainage, closure and drainage, proximal colostomy, either alone or with drainage, and exteriorization, either alone or combined with one or more of the preceding, all

have their staunch advocates. Should the patient die after one of these preliminary operations, it is generally reasoned that to do more would be tantamount to certain death. However, the comparative clinical data presented do not give credence to this a priori form of reasoning. Similarly, the clinical results of others are in support of primary resection in the treatment of perforations of the colon.

Belding reported 4 patients with diverticulitis of the sigmoid colon with perforation and diffusing peritonitis, 3 of whom were treated by primary resection and end-to-end anastomosis. In each, the recovery was complete and uncomplicated. In the remaining patient, the perforated diverticulum was resected and a two layer closure of the opening in the colon was performed. Witowski and associates reported 2 patients with perforated lesions of the right side of the colon and abscess formation, in each of whom a right hemicolectomy with primary anastomosis was performed. There were no postoperative complications. Ryan (13) reported 4 patients with perforations of the left side of the colon and diffusing peritonitis who were treated by primary resection and anastomosis. Each of the patients recovered. Subsequently, 2 patients with diverticulitis of the sigmoid colon, perforation, and diffusing peritonitis were treated by one stage and two stage resections respectively (14). The first stage of the two stage procedure was a Hartman anterior resection with proximal terminal colostomy and inversion of the intraperitoneal distal transected end. Approximately 7 months later, colon continuity was restored by an intraperitoneal end-to-end anastomosis, and a completely satisfactory result was obtained.

Judd and Goligher (7) have each treated 2 patients with diffusing peritonitis secondary to perforated diverticulitis of the sigmoid colon by primary resection and immediate anastomosis without any morbidity or mortality. Gregg performed primary resections for acute perforations of the colon in 9 patients, 7 with diverticulitis and 2 with cancer, none of whom died. Donaldson (5) reported a series of 22 patients, 2 with a free perforation and diffusing peritonitis and 20 with local (abscess) peritonitis, treated by primary resection. One, or 4.5 per cent, of the 22, a patient with a free perforation of a cancer of the splenic flexure, died (6).

The collected series presented numbers 46 patients with perforations of the colon and peritonitis, either local (abscess) or diffuse, all but 1 of whom were treated by primary resection and anastomosis. The 1 exception was the patient treated by a two stage primary resection. One of the 46 patients died, a mortality rate of 2.1 per cent. When this collected series is combined with the present series reported, the total is 56 patients with perforations of the colon and peritonitis, either local or diffuse, treated by primary resection. Two of the patients died, a combined mortality rate of 3.5 per cent.

In contrast to primary resection, the results obtained by the use of multistage operations in the treatment of perforations of the colon have been less encouraging. A notable exception is the series reported by Smithwick in which 8 patients, 2 with diffusing peritonitis and 6 with abscess formation, were treated by resection of the colon in three stages. None died. Contrariwise, Brown and Toomey, in a study of 258 patients with diverticular disease of the colon, reported 53 patients with perforations of the colon treated by preliminary or first stage operations. Twenty-three of these patients died, a mortality rate of 43.4 per cent. This is comparable to the similar results reported in this study, namely, 36.2 per cent. In 17 of the 53 patients a proximal colostomy was performed and 9 patients, or 53.0 per cent, died. In 28 of the remaining 36 patients, one of the following operations was performed: simple drainage, closure of perforation and drainage, cecostomy, and finally exteriorization. Thirteen of this group of patients died, a mortality rate of 46.4 per cent.

Goligher and Smiddy (8) reported 52 patients with cancer of the colon, perforation and peritonitis, either local or diffuse, treated

by suture of the perforation combined with cecostomy or colostomy. Forty, 76.9 per cent, of these patients died. In comparison, 21 other patients in the same category were treated by primary resection and only 5, or 23.8 per cent, died.

Although it may be maintained that the high mortality rate in the treatment of perforations of the colon by multistage operations is due to the fact that the patients are more gravely ill, this is not believed uniformly applicable. It is frequently stated: "The patient was too ill to withstand other than the minimum emergency surgical procedure." From the results of the present study and those of others as previously presented, it is believed that this statement may be paraphrased to read: "The patient was too ill to withstand other than a primary resection."

The rapidity of clinical improvement and the lessened morbidity observed in the patients immediately after primary resection compared with the patients after a preliminary or first stage procedure have been most impressive. From such observations it became immediately apparent that the removal of the source of the contamination was the basic underlying factor in the improvement.

From a review of the results of our experience with both primary resection and multistage operations in the emergency treatment of perforations of the colon, it is believed that primary resection is the preferred method of treatment. We are in complete accord with the logic and support the concept expressed by Crile: ". . . it is the disease, not the operation, that causes death, and the first responsibility of the surgeon is to eradicate the disease."

CONCLUSIONS

In perforated lesions of the colon with either local (abscess) or diffusing peritonitis, primary resection is a feasible operation and is the preferred method of treatment.

When the perforation is a complication of cancer of the colon, primary resection is in general believed mandatory.

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EDITORIAL

CO-OPERATION, NOT COMPETITION, IN THE MANAGEMENT OF CANCER OF THE CERVIX

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ONE OF THE TRAGEDIES of cancer of the cervix is that the patient may be shuttled between different specialists, each of whom disclaims responsibility for more than a fragment of her body, and to none of whom she can easily turn for comfort. Even when the outcome of treatment is successful it is not uncommon for a patient to come successively under the care of a general practitioner, a gynecologist, and a radiologist. When the result is less fortunate the special services of a chemotherapist, general surgeon, neurosurgeon, pathologist, proctologist, or urologist—to name but some—may be required in addition. Unless careful direction is exercised it is easy for the patient and her family to become confused in the midst of so many experts.

The problem is how to co-ordinate the special skills of modern medicine in the best interest of the patient with cancer of the cervix. There is no doubt that in certain instances the knowledge acquired in the above nine or more special fields may be necessary for the best care. And yet one would hardly think of the neurosurgeon, for example, as being the most appropriate co-ordinator.

At the present time the two physicians who are most concerned are the gynecologist and the radiologist. It is with these two that the organization of co-operation should start. This may take two forms—in the management of patients and in the training of specialists.

Of first importance is agreement as to the steps to be taken for the diagnosis, workup, and evaluation of patients with cancer of the cervix. This sort of co-operation can be strengthened in a given community by combined rounds and combined discussion of all patients through a pelvic cancer clinic or pelvic cancer service. In private practice the admission to hospital of patients with cervical cancer for a standardized preliminary workup, staging, and initial management can do much to encourage co-operation. By mutual agreement, then, the follow-up of such patients can be arranged so that the special knowledge of each physician is used to the best advantage. It does not matter whether the radiologist or the gynecologist is the prime mover in setting up such a program, provided that he is willing to let it be really co-operative. It is essential that the patient be told, as soon as she is seen, of the importance of both physicians seeing her and deciding the best treatment for her. She must understand the plan of management and know whom she should consult if she has difficulties. Within such a framework, clearly established, the employment of consultants can be readily arranged.

From the Department of Obstetrics and Gynecology, University of Mississippi School of Medicine, Jackson.

If co-operation is to be achieved in practice, then it must start during training. Although the time available in the standard 3 year residency in radiology or in obstetrics and gynecology can permit only a superficial acquisition of skills in the various aspects of management in cancer of the cervix, much can be achieved by insuring co-operation between the two departments. For example, at the University of Mississippi Medical Center, combined rounds are held twice weekly between the two departments. At these we discuss the diagnosis, staging, and therapy of all new patients with cervical cancer as well as other malignant pelvic tumors and carefully review together all old patients who present problems. The insertion of radium is also a combined procedure between the two departments. However, more than this is needed. The institution of post-residency fellowships in the management of pelvic cancer might do much to supply the need. Depending upon the main interest of such a fellow, whether it be in radiology or gynecology, he should, in the course of this additional training on an active pelvic cancer service, be able to acquire the basic principles, if not all the technical details, of patient care in fields outside his own. He should also learn the absolute necessity of co-operation with other specialists involved in the management of these patients and of the methods by which such co-operation can be obtained.

The co-operation of radiologists and gynecologists has been emphasized. No one would consider that the ideal treatment for cancer of the cervix has yet been found. In the future, chemotherapy may have much to offer. As new discoveries are made, the chemotherapist may become an important part of the team managing patients with cancer of the cervix. But in the meantime, it is essential that the patient be given the benefit of all the knowledge available rather than that her care be limited to that provided by the radiologist or gynecologist alone.

THE SURGEON AT WORK

A LOW PRESSURE GASTROINTESTINAL SUCTION APPARATUS FOR NEONATAL SURGERY

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THE IMPORTANCE of gastrointestinal decompression after neonatal surgery has been repeatedly emphasized. However, adequate decompression cannot be maintained in the newborn with the usual suction apparatus used in adults. Even the lowest pressures provided by standard suction machines invariably cause plugging of the tube openings by gastric mucosa. These pressures, from minus 70 to minus 90 millimeters of mercury, are 4 to 5 times greater than that necessary to decompress adequately the stomach of a newborn. In order to overcome this problem, special low pressure suction machines have been constructed. Thomson used a different approach by devising a gastric tube with an inflatable balloon between the suction holes to keep the mucosa away. Unfortunately, special tubes and suction apparatus are not available in many hospitals.

The purpose in this communication is to describe a simple arrangement which provides the optimum negative pressure as well as a collecting system for accurate measurement of gastrointestinal losses. This low pressure system

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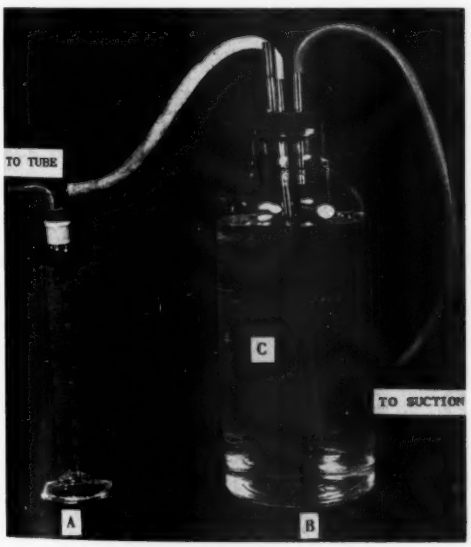

FIG. 1.

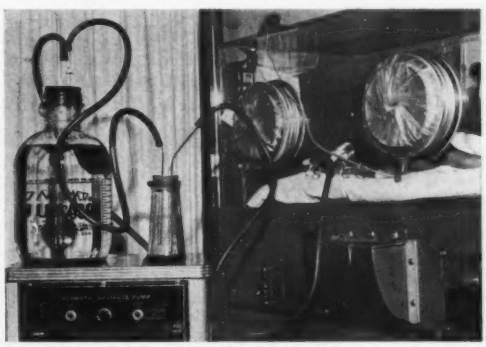

FIG. 2.

FIG. 1. Apparatus ready for use. *A*, Small graduate for accurate measurement of fluid losses. *B*, Bottle from chest drainage set filled with water. *C*, Tube set 15 to 25 centimeters below water level and open to atmosphere. This regulates the negative pressure in the otherwise closed system.

FIG. 2. Low pressure gastrointestinal suction apparatus in use in newborn after correction of duodenal atresia.

will also prevent the danger of gastric perforation which Potts has described as occurring when a standard suction machine is used.

The necessary components are available in any hospital and are usually part of a 2 or 3 bottle chest suction apparatus. These components are: (1) a large bottle at least 25 centimeters high with a 3 hole stopper; (2) a small graduated tube or flask with a 2 hole stopper—a graduated urine bottle may be used if nothing better is available; and (3) connecting rubber and glass tubing.

These are connected as shown in Figure 1. The center tube in the large bottle is placed so that 15 to 20 centimeters of its length are below water level, thus setting the negative pressure in the system at minus 15 to 20 centimeters of water. This has been found to be the optimal pressure in newborns, the lowest pressure which will empty the stomach of air and fluid. Any intermittent or continuous suction source may be used. Minimal lengths of rubber tubing are advisable. Figure 2 shows the apparatus in use after correction of duodenal atresia.

SUMMARY

A simple suction system is described which provides optimum negative pressure for the newborn. The need for special low pressure suction in this age group is emphasized.

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A SIMPLIFIED MEDIAN STERNOTOMY INCISION

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THE USE of a median sternotomy as the incision of choice to expose the mediastinal structures for extracorporeal circulation or open repair of cardiac anomalies seems well accepted. This type of incision for mediastinal tumors, pericardiectomy, and some closed procedures upon the heart or great vessels is also utilized by Holman, Julian, Lillehei, and their associates.

The technique of this incision has been described in detail by several surgeons. Most mention the use of a power saw or Lebsche knife or other bone-cutting instruments to divide the sternum.

The trauma and difficulties sometimes encountered with the use of a Lebsche knife are not acceptable to many surgeons. The use of a power saw has caused lacerations in the enlarged right ventricle which is present immediately beneath the sternum in many patients being operated upon for congenital or acquired cardiac defects.

The insertion of wires to approximate the divided sternum is, at times, difficult, particularly in the older patient with a more heavily calcified and thicker sternum.

A technique which has been used in over 150 median sternotomies and has proved simple, safe, and rapid is described herein.

The skin of the thorax, upper portion of the abdomen, and neck is prepared and draped in the suitable manner. A median skin incision is made from 3 to 4 centimeters below the jugular notch to 4 to 5 centimeters below the area of the xiphoid process. Bleeders are coagulated, and the remainder of the incision is made with electrocautery. By elevating the superior angle of the skin incision, the upper border of the manubrium is exposed, and the jugular notch is visualized. Placing the skin incision in this manner and undermining the upper angle of the incision allow the scar to lie lower and improve the cosmetic appearance. The xiphoid is then divided by cautery in the midline, and a finger is inserted into the anterior mediastinum. The pleura is swept aside, first by the finger and then by a peanut sponge held on a long, curved clamp. The Gigli saw guide (Fig. 1) is easily passed behind the sternum until the tip of the guide is seen between the heads of the strap muscles in the jugular notch. The Gigli saw is placed in the eye of the guide and withdrawn from beneath the sternum (Fig. 2). The eye of this guide is made in such a manner that neither edge protrudes, and, consequently, soft tissue cannot be hooked by the guide. The division of the sternum by use of the Gigli saw is rapid and simple. A clamp is placed across the sternum by an assistant at the site where the Gigli saw wire will cut through the sternum (Fig. 3). Thus the wire is prevented from suddenly straightening out as it cuts through the sternum. Bone wax applied to the cut ends of the sternum easily controls the bleeding from the marrow cavity. The anterior and posterior surfaces of the periosteum of the sternum are carefully coagulated with electrocautery.

In the younger child, the sternum is simply divided with a pair of bandage type scissors, with the flat point on the lower blade passed beneath the sternum to prevent injury to the underlying structures.

The closure of the sternal incision is greatly aided by the sternal awl. The point of this awl is easily inserted through the sternum. Braided steel wire is passed through the eye, and the awl is withdrawn (Fig. 4). The eye of this awl is large enough to allow simple threading, and still small enough that the hole made in the sternum does not produce a troublesome bleed-

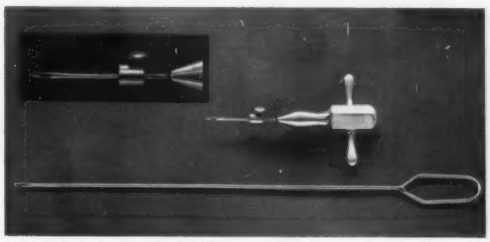

FIG. 1. A photograph of the sternal awl and Gigli saw guide. Inset discloses a close-up of sternal awl point and locking vise to determine depth of penetration of needle.

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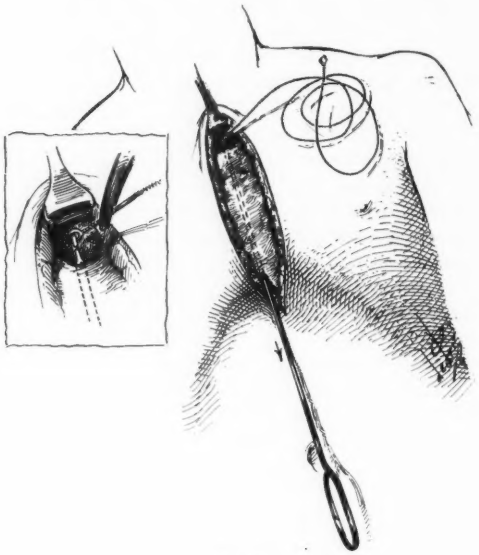

FIG. 2.

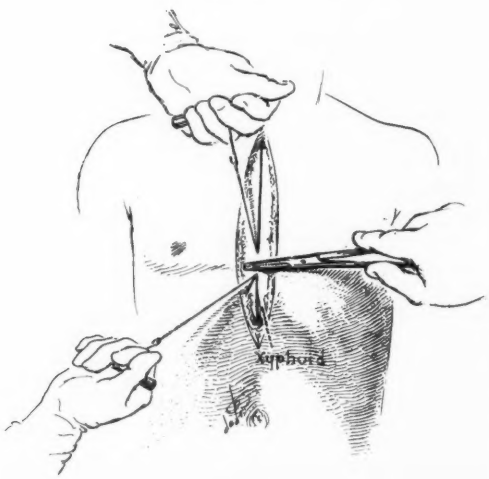

FIG. 3.

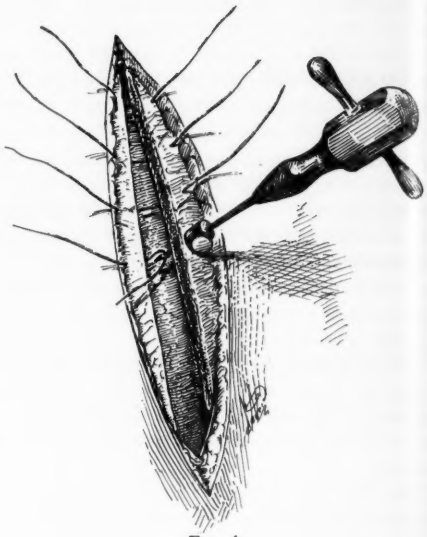

FIG. 4.

FIG. 2. The guide for the Gigli saw is passed beneath the sternum after the areolar tissue has been swept aside. The guide is then easily withdrawn, bringing the Gigli saw beneath the posterior table of the sternum.

FIG. 3. The sternum is rapidly and simply divided with the Gigli saw. Care is being taken to keep the saw in the midportion of the sternum.

FIG. 4. Braided No. 0 wire is utilized to approximate the sternum. Heavy silk or other nonabsorbable suture material may be used.

ing point. The needle point of the awl is threaded into the awl handle to allow the selection of different sized needles as well as replacement, should a needle become broken or bent. A lock nut on the shaft of the awl allows one to control the depth of penetration of the needle. After all the wires have been inserted, the sternum is approximated by tying the lowermost wire, while the next higher one is held crossed. In this step-like manner, the sternum is then closed from the lower angle to the upper angle. Chromic sutures are placed in the strap muscles, and these are tied after the wires in the sternum have been tied and cut. The ends of the wire are twisted and buried. The rest of the wound is closed with catgut, and the skin is closed with a subcuticular catgut suture to complete the closure of the median sternotomy incision.

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The Book Shelf

MEDICINE IN NUMISMATICS

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COINS of medical significance have been used by various groups and governments since ancient times. The basic reasons for coins of this nature, especially among the early civilizations, have been fears and superstitions. Invocations to the gods and to the unknown were frequently inscribed on coinage. The problems, hopes, fears, and aspirations of daily living of the people were often portrayed in this manner. The ancient Greeks and Romans were unusually prolific in this field and for several centuries minted many coins of this type.

GREEK AND ROMAN ERA

Many medical and health inscriptions, signs, and subjects have been recorded (4). The most frequent subjects and the most pressing problems portrayed on coinage were mice or flies signifying pestilence or other epidemic diseases, locusts signifying famine, baths or mineral springs for health-giving qualities, sewage for sanitation, the poppy for pain, the pomegranate for intestinal worms and gynecologic difficulties, and the cupping glass for illness. The omphalos or navel was often portrayed. However, its exact medical significance is not clear. The laurel was often portrayed for the medicinal virtue of music. Many gods were portrayed, chiefly Dionysus and Bacchus emphasizing the medicinal value of wine; Aesculapius, Salus, and Hygeia for healing and Telephorus for convalescence. Other gods and demigods and mythologic characters, inscriptions, and symbols dedicated to marriage, pregnancy, fertility, children, love, longevity, wisdom, and other phases of daily life are also frequently found on coins of this period.

MAGATAMA, CHILDBEARING COINAGE FROM PREHISTORIC JAPAN

About this same period, embryo-shaped stone pieces known as "magatama" (2) were used as coinage in prehistoric Japan. They were made of jade, agate, or malachite. These pieces varied in size from approximately ¾ inch by 1 inch to about 2 inches in length. Those found today are of various colors and often very beautiful. The piece illustrated is of agate (Fig. 1). Many fine specimens have survived intact to the present time. Most of the evidence today

FIG. 1. Childbearing or magatama coin from prehistoric Japan.

FIG. 2.

a b

FIG. 3.

FIG. 4.

FIG. 2. Chinese silver dollar of 1837 portraying the god of longevity. Known as the "old man" piece.

FIG. 3. Pesttaler minted in 1520. a, Head or obverse. b, Reverse.

FIG. 4. Leper colony coin. Issued by the Phillipine Health Service for use in the Culion Leper Colony and leper health stations.

points to their use as a protection in childbearing. Historians, although agreeing that these pieces were used as coinage, differ as to their meaning. Some believe that these pieces are shaped to resemble a claw of some animal, possibly a tiger. This assumption has some basis as the tiger's claw is one of the strongest amulets in the Orient.

LONGEVITY

Longevity has long been stressed on coins in the Orient, especially China and Japan. For a period of over 1,000 years, longevity has been periodically depicted on various coins as an aged individual with a bent back and considerable hair on the body. The first modern Chinese silver coinage (1) is characterized by the portrait of the god of longevity who is shown as bearded and aged. These coins exist in many varieties. The piece illustrated (Fig. 2) is from China and was minted in 1837. The issue was struck by the Emperor Tao Kwang to finance a campaign to fight a revolution against him on Formosa. The coin is often referred to as the "old man" piece.

PESTTALER

The medieval period with its ignorance and superstitions produced many religious charms and amulets as a defense against the frequent epidemics which devastated whole populations. By the sixteenth century, coins were issued for this purpose. The most famous coins were the pesttalers minted at the mining town of Joachimsthal in Bohemia. This community was a famous medieval center known for the production of artistic religious medals. The coin illustrated (Fig. 3) was minted in 1520. The face or obverse shows St. John crucified among his followers within an inscription. The reverse shows Aesculapius among the sick. The coin was also issued in double talers and fractions of talers. In ancient and medieval times, the expression "plague" meant pestilence of any kind and referred to any contagious disease and not necessarily bubonic plague. Smallpox, cholera, and yellow fever were also devastating and common. These diseases resulted in a high mortality. The outbreaks were frequent and sudden, destroying large populations and producing panic among the helpless and superstitious peoples. The

FIG. 5.

FIG. 6.

FIG. 5. Ten franc note from the Saint Amedeus Insane Asylum at Mortsel, Belgium. The denomination—Tien Frank and Dix Francs—is printed on the face.
FIG. 6. "Gizzi penny." The coin with a soul.

talers were frequently worn around the neck as a charm against these epidemics. Although most of the talers were minted at Joachimsthal, mints in other cities produced them. Many are very artistic and excellent examples of the engraver's art.

BLIND MAN'S NICKEL

In 1882, the United States Mint officials contemplated a special coin for the blind, designed for easy recognition. The coin, a 5 cent piece, never went beyond the pattern stage as it was not accepted by Congress for regular coinage. Several of the patterns are in numismatic collections today. Both sides of the coin have the same design as the regular shield nickel of the period. The distinguishing features are 5 bold ridges on the edge separating the edge into 5 exactly equal segments. Whether it was the actual purpose of the United States Government to issue a special coin for the blind has never been fully determined from the official records. However, only a few months after the patterns were minted, statements appeared in the numismatic literature that the coin was specifically made for the use of the blind. If so, a denomination in most common use and which undoubtedly would satisfy the requirements of the majority of financial transactions of daily living would be the logical one selected. Apparently in 1882, the 5 cent piece represented the most widely used denomination. Today, the 5 cent piece purchases little.

It is not known why the design was not accepted. However, it was probably very obvious to the majority of the members of Congress that it was very simple to distinguish the various regular denominations merely through the sense of touch.

LEPER COLONY COINS

For the first half of the twentieth century, various governmental agencies issued special but official coinage for use in the leprosy colonies under their jurisdiction. The purpose was to prevent contamination of others by the lepers. When it was found that leprosy was not transmitted through the coins and that it was more humane to treat these people as sick and not to be isolated from the world, the special coinage was discontinued. The most extensive coinage was used by the Culion Leper Colony in the Philippine Islands. This colony is still in operation. Special coinage issued in 1913 was discontinued sometime before World War II. The first issue was of aluminum, but because of the corrosive action of the disinfectant and the rapid deterioration of aluminum in the tropics, later issues were of an alloy of copper and nickel. The coin illustrated (Fig. 4) is one peso of copper-nickel. These coins were issued by the authority of the Philippine Public Health Service. On the head side, or obverse, was often the portrait of a Filipino patriot, usually José Rizal, a physician. Surrounding the portrait was the legend, Culion Leper Colony, Philippine Islands. On the tail side, or reverse, was the insignia of the Philippine Health Service, with the legend, Philippine Health Service, denomination, and date. The denominations ranged from ½ to 20 centavos and 1 peso. They were legal tender to be used in the leper colony or in the leper hospitals or stations in the Philippines. Another leper colony was the Nagashima Leper Colony in Japan, which also used its own currency. This currency was used in various denominations corresponding to our values from cent to dollar. These were issued by the Nagashima Department of Health and were discontinued shortly before World War II. The

leper colony maintained by the Venezuelan Government on Providence Island on Lake Maracaibo issued its own coins in 1913. These were struck in brass, varying in size according to the denomination. The head or obverse bears the word "Lazaretto Nacionale Maracaibo 1913." The reverse has its value represented. The largest is 20 bolivars and the smallest, ⅛ bolivar. Its use was discontinued after a short period. The MacKean Leper Colony in Chiengmai, Thailand, did not issue a special currency but altered the established coinage of the country by filing a deep groove across the regular coins. Coins with the grooves were used only by the lepers and avoided by the other residents of the community. Coins were also issued by the United States Government for use at the Palo Seco Hospital in the Canal Zone from about 1919 until 1952. These coins ranged from 1 cent to 1 dollar. The 1 to 5 cent denominations were in brass with a square hole; the 10, 25, and 50 cent pieces, and 1 dollar pieces were aluminum with a round hole. On one side was inscribed "Palo Seco Canal Zone." On the other side "Redeemable for . . . [denomination as 5 cents with the numeral] in merchandise." All coins on hand were destroyed by melting by the United States Government in 1952.

INSANE ASYLUM COINS

Special and unofficial coinage and currency (Fig. 5) were issued for the inmates of various mental institutions in Europe, especially Belgium and France, during the early 1900's. They were usually issued by religious organizations. Their use in the majority of cases was discontinued before World War II.

COIN WITH A SOUL (GIZZI PENNY)

An interesting coin (Fig. 6) although not of actual medical significance is included in this series. Up until very recently, it was used by various tribes of Africa (3), chiefly by the Gizzi tribe. It is still used to a limited extent in the western provinces of the Liberian hinterland. This coin is a long handwrought iron piece with a tail and wing and from 15 to 18 inches in length. It is known as a Gizzi penny. If broken, the "soul" escapes and the coin is no longer current or of value until reincarnated by the medicine man of the tribe. A fee is necessary for the reincarnation and only a medicine man can perform this duty. Reincarnated specimens are noticeable by a slight irregularity at the point where the coin was broken. In the 1930's, 60 pennies were worth about 24 to 26 cents. Two pennies would buy 20 oranges or a bunch of bananas.

Much can be learned from the coinage of a nation. Often the entire medical or epidemiologic history of a people, as the ancient Greeks and Romans, can be found recorded in a lasting manner through its coinage. In recent times, leper colony and insane asylum coins record an era of treatment, namely separation and isolation. The discontinuation of this coinage reflects our changing approach and treatment of diseases.

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Reviews of New Books

Clinical Disturbances of Renal Function. By ABRAHAM G. WHITE, M.D., F.A.C.P. 439 pages, 83 illustrations. $10.50. Philadelphia and London: W. B. Saunders Co., 1961.

Reviewed by WILLARD E. GOODWIN

MOST of the important points concerning clinical renal dysfunction are covered in a concise and helpful manner in *Clinical Disturbances of Renal Function*. The author, Abraham G. White, has done an admirable job of presenting the major facts of renal disease in terms of current physiologic knowledge.

Important chapters include the following subject matter: nephritis; the nephrotic syndrome; hypertension and renal dysfunction; acute renal failure; obstetric, surgical, and urologic aspects of renal dysfunction; cardiopulmonary influences on renal function; cirrhosis; hormonally induced disturbances; and an interesting chapter on the neuropsychiatric aspects of renal dysfunction. The last 2 chapters deal with the therapeutic use of water and electrolytes and a review of the various clinical methods for evaluation of renal function. There are 3 brief but valuable appendices on renal anatomy, renal transport mechanisms, and the pharmacology of diuretics.

The author describes the clinical picture of most important renal diseases and associated states that affect renal function and then proceeds to tell the reader what to do about them. The book is particularly useful because of a carefully selected bibliography at the end of each chapter. It could become a kind of necessary handbook of renal disease, consulted often by students and by clinicians who are faced with clinical problems of renal dysfunction. The surgeon and the urologist will find valuable information and advice, particularly regarding renal function in relation to surgery. "Medical renal groups" should find much authoritative information in its pages.

Diagnostic Cytology and Its Histopathologic Bases. By LEOPOLD G. KOSS, M.D., with GRACE R. DURFEE, B.S. 360 pages, 776 illustrations. $16.50. Philadelphia and Montreal: J. B. Lippincott Co., 1961.

Reviewed by LAUREN V. ACKERMAN

THIS BOOK entitled *Diagnostic Cytology and Its Histopathologic Bases* is the only one of its type. It can be used profitably with the *Papanicolaou Atlas*. However, it provides a good framework of reference for the pathologist and the cytology technician. It appropriately emphasizes respiratory and female genital tract cytology but also gives all the up-to-date information on other areas, such as the gastrointestinal tract, and presents the cytology of effusions as well. The chapter on aspiration biopsy smear was written by John W. Berg. Also, there are chapters on cytologic techniques and suggestions for the proper organization of a cytology laboratory. There is a short general introductory section on cytology which will be of utmost interest to the cytology technician.

The photomicrographs prepared by the associate author, Grace R. Durfee, are of good quality and were carefully selected. These illustrations along with the clinical histories point up the important diagnostic points and are also used to illustrate the areas of greatest difficulty and the types of lesions which could be incorrectly interpreted. The authors have had an extensive practical experience, and it is this background of experience which makes the book so valuable. The tremendous value of cytology has been emphasized throughout, but conservatism has also been stressed within the limits of practicality. The various cytologic patterns are correlated, frequently with photomicrographs of tissue sections. The bibliography has been carefully selected to supplement the text. This publication can be recommended without reservation to cytologists and pathologists.

Die Erkrankungen der Gallenwege und des Pankreas. By DR. WALTER HESS. 660 pages, 266 illustrations. $35.50. Stuttgart: Georg Thieme Verlag, 1961.

Reviewed by KAREL B. ABSOLON

A CLEARLY WRITTEN account of gallbladder and pancreatic diseases is given in *Die Erkrankungen der Gallenwege und des Pankreas*. Either of the subjects would be considered overwhelming by the average author. Hess was able to interpret the surgical physiology, pathology, and treatment of the liver, biliary tract, and pancreas in appropriate detail. His writing has resulted in a didactic monograph, as well as a valuable reference text. Its arrangement is one of systematic analysis in the style of classical medical writings, but it does retain a breath of refreshing originality. The anatomic, physiologic, and pathologic analyses are followed by the clinical problems encountered.

The anatomy of the portal area is described, but not to such an extent as to lose the reader in unnecessary and undigestible detail. Careful dissection in discerning anatomic variations, the prime credo of the operating surgeon, is restressed. Cholecystitis and cholelithiasis remain prominent clinical problems. The recognition of chronic inflammation of the papilla of Vater is emphasized and 3 pathologic types are recognized, namely, the inflammatory sclerosing type, the fibrocystic type, and the adenomyomatous form. The consequences of common duct obstruction are outlined, such as hepatic parenchymatous complications, internal fistulas, and periductal inflammations.

The value of laparoscopy, laparoscopic cholangiography, and percutaneous cholangiography is evaluated. The laboratory tests for hepatic, extrahepatic biliary, and pancreatic diseases remain adjuncts to proper clinical evaluation.

The chapter on the differential diagnosis is instruc-

tive. Postoperative complications in the therapy of gallbladder, common duct, and pancreatic diseases are well summarized. However, it is rather difficult to see why the archaic concept of the "hepatorenal syndrome" should be reviewed. The electrolyte and water balance problems in biliary and pancreatic diseases are outlined briefly but effectively.

The author's surgical experience of the anatomic area under discussion is well expressed and tabulated.

The pictorial presentation of the operations is instructive and an asset to the book. The author mentions the various operative procedures but takes a stand as to his preferences.

The reproductions of roentgengrams and of the very fine illustrations are in line with the tradition of the Thieme publishing company.

This scholarly volume will find its way into medical libraries and onto the bookshelves of those engaged in surgery of the abdomen.

A System of Medical Hypnosis. By AINSLIE MEARES, M.D. 484 pages, $10.00. Philadelphia and London: W. B. Saunders Co., 1960.

Reviewed by FRED. T. KOLOUCH

THE UTILITY OF HYPNOSIS in surgery was established by Braid, Esdaile, and others more than a century ago. Later, interest in hypnosis dwindled with the advancement of pharmacology and the development of chemoanesthesia. Currently, hypnosis is enjoying a renaissance, probably related to the psychosomatic approach to the treatment of organic illness and the recognition of the limitations and, sometimes, dangers of drugs.

The surgeon interested in hypnosis can find a fascinating, practical, and thoroughly understandable evaluation of this modality in Meares's book. It is the culmination of his personal experience in psychiatric practice. Although written by a psychiatrist, it offers the surgeon a useful and comprehensive view of modern hypnosis. The text is extremely well organized and lucidly written, clarifying the various aspects of hypnosis in a precise, orderly fashion.

A System of Medical Hypnosis is presented in 5 principal segments: (1) the nature of hypnosis, (2) the induction of hypnosis, (3) suggestive therapy, (4) hypnoanalysis, and (5) hypnosis in general medicine. Sections 1, 2, 3, and 5 all contain information useful to the surgeon interested in the application of hypnosis to surgical patients.

Meares's theory concerning the nature of hypnosis is very attractive. He makes the psychodynamics of the trance state quite comprehensible and explains the nature of hypnosis as an atavistic regression depending upon the concept that suggestion is an archaic mental function.

His sections on motivation, the doctor-patient relationship, choice of methods of induction, moral and ethical aspects, and induction methods introduce one to the problems of the induction of hypnosis and the simplicity of their solution. The section describing the dynamic method of induction of hypnosis is especially helpful.

The variety of applications of suggestive therapy reveal many useful facets related to the practice of surgery. His candid elucidation of the limitations and dangers of hypnosis in this field should be memorized by anyone interested in using suggestive therapy.

The ultimate use of hypnosis in surgery is related to the control of preoperative fear and anxiety and postoperative discomfort. The sections on hypnosis and relief of pain, hypnosis as an anesthetic agent, and hypnosis in gynecology show the effectiveness of the technique in this sphere.

Meares is confident that hypnosis has a bright future in medical therapy. He believes that, with a bit of understanding of psychodynamics and a more critical selection of cases, many more patients could be helped through suggestive therapy. Greater general use could be made of nonspecific suggestions and the educative value of the hypnotic experience. He also believes that there is a place for the general use of hypnosis as an adjunct in surgery, and states, "We see a revival of the use of hypnosis in anesthetics, particularly in dentistry. Other than in exceptional circumstances, there is little place for unaided hypnosis as an anesthetic agent in surgery. . . . On the other hand there seems to be a wide scope for the greater use of hypnosis, both preoperatively and postoperatively, and relaxing techniques and hypnoidalization could save much pain in the minor procedures of office practice."

Meares decries the lack of opportunity for medical training in hypnosis. In an idealistic conclusion to the book, he suggests that beyond his technicologic achievements a physician must somehow help his patient to achieve a sense of purpose and individual dignity. He asks, "Can hypnosis achieve such a goal?" In reply he states, "We can help the patient to sleep without sedation, to feel calm without tranquilizers and to experience pain without the hurt of it." He also asks, however, "Can we help him to fulfill his biological heritage of love and aggression to the benefit of both himself and those around him?" This, Meares believes, is a distant horizon.

The Conquest of Pain; Achievements of Modern Anaesthesia. By RONALD WOOLMER, M.D. 240 pages, illustrated. $4.50. New York: Alfred A. Knopf, 1961.

Reviewed by MAX S. SADOVE

THIS MONOGRAPH by Ronald Woolmer is an interesting collection by a very scholarly teacher. It is the story of the anesthesiologist's activities in relation to the modern hospital. It is not, as the title would imply, the history of anesthesia or even of the management of pain, but rather an interesting, simply and concisely written story of the activities and interests of the anesthesiologist.

It can be unhesitatingly recommended to the anesthesiologist, the medical student, and the nursing group because of its broad scope. It is of value to the library that collects books of rather broad scope, and especially to those individuals who would like to know exactly what it is that the anesthesiologist does. The book is easy to read, informative, and enjoyable.

Die chirurgische Behandlung der angeborenen Fehlbildungen. Edited by Priv.-Doz. Dr. K. KREMER. 592 pages, 349 illustrations. $29.50. Stuttgart, Germany: Georg Thieme Verlag, 1961.

Reviewed by PETER P. RICKHAM

THE BOOK on *The Surgical Treatment of Congenital Malformations* was written by Professor Derra's pupils in honor of his sixtieth birthday. It is beautifully printed and the illustrations are of a high standard.

After the last war Derra founded what became the most important cardiac unit in Germany in Düsseldorf, and it is therefore not surprising that approximately a third of the book deals with cardiovascular abnormalities. This is the best part of the book. The treatment of most of the common cardiovascular abnormalities is described, and, although there is little new or original, these chapters are up-to-date, and the literature quoted contains most of the more important Anglo-American contributions to this subject. There is no mention of diagnostic procedures, and the description of techniques is brief. Since Düsseldorf is the leading school in Germany for cardiovascular surgery, it seems curious that this part of the book was not enlarged and written as a reference work for German chest and pediatric surgeons interested in the subject.

Instead, the authors have included descriptions of some other congenital malformations. These chapters are short, with few references, and recent developments in the English-speaking countries are largely ignored.

Insofar as American and English surgeons are concerned, the opinions expressed and the operations described for genitourinary and neurosurgical malformations appear to be somewhat out of date. The German speaking surgeon, acquainted with the publications of such leaders in pediatric surgery as Grob and Rehbein, must be disappointed in the contents of this book, with the exception of those portions dealing with cardiac surgery.

Surgery of the Anus, Rectum, and Colon. By J. C. GOLIGHER, Ch.M., F.R.C.S. 829 pages, 531 illustrations. $35.00. Springfield, Ill.: Charles C Thomas, 1961.

Reviewed by WILLIAM C. BERNSTEIN

IN 1877, Joseph MacDowell Mathews of Louisville, Kentucky, journeyed to England to learn what he could of diseases of the rectum and colon at St. Mark's Hospital in London. He returned to America and became the first proctologist on this continent. Since that time American surgeons have continued to learn and be inspired by the English surgeons who have been pre-eminent in the field of colon and rectal surgery. Once again, through the publication of Goligher's new book on *Surgery of the Anus, Rectum, and Colon*, American surgeons are greatly indebted to their English colleagues.

J. C. Goligher, who holds the Chair of Surgery at the University of Leeds but who received most of his training in London, has written what is, in this reviewer's mind, an outstanding text in the field of colon and rectal surgery. The volume is as refreshing as it is inspiring. Goligher is fair in evaluating the published work of others, but he does not hesitate to speak out when he believes that a change in thinking is necessary. He takes exception, for example, to the time-honored idea that the external anal sphincter muscle is composed of 3 distinct bundles, and he sounds the death note for the white line of Hilton—a long overdue step in the right direction.

Goligher has been careful in describing techniques of both examining the patient and carrying out operative procedures. The surgical anatomy of each operation is made clear to the reader by means of words, drawings, and photographs. The chapter on fistula-in-ano is unusually complete and is presented in an interesting manner. This chapter, in particular, includes a comprehensive historical background.

Tumors of the colon and rectum constitute 305 pages of this 829 page book. The author brings the reader up-to-date on all phases of the subject and then proceeds to fulfill the requirement of an excellent teacher by stating in definite terms, "This is how I do it." The chapter on ulcerative colitis is also an excellent presentation of a large and difficult subject.

For the surgeon in training or for the active surgeon who frequently encounters difficult problems in the field of colon and rectal surgery, this book is highly recommended.

The Closed Treatment of Common Fractures. By JOHN CHARNLEY, B.Sc., M.B., F.R.C.S. 269 pages, 215 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1961.

Reviewed by FRANK E. STINCHFIELD

IN AN ERA in which the operative treatment of fractures frequently receives untoward precedence, it is a pleasure to welcome John Charnley's third edition of his now famous monograph to the list of classic texts which should be included in the library of every fracture surgeon.

In his introduction, Charnley indicates that his purpose is to clarify the principles of fracture reduction for the young resident, inexperienced and untried, who, all too often, is the first to see and treat the injured patient. It is to this house officer that the golden opportunity for definitive treatment is presented. An understanding of the basic principles of the role of soft tissues as well as bone in the reduction, maintenance, and repair of fractures, so clearly outlined in the early chapters, enables the casualty officer thoroughly to understand the basic pathomechanics and the aims of closed manipulation. The principles so clearly illustrated by Charnley's lucid prose and by the excellent illustrations are applied to each fracture in succeeding chapters so that the theme of the text is held in simplified continuity throughout the monograph.

As might be inferred from the title of his text, Charnley is, nevertheless, by no means iconoclastic in his attitude toward open reduction. Its unwarranted use is decried, however, and its pitfalls are amply illustrated by basic references to the effect

of periosteal stripping and associated soft part trauma inflicted upon an already injured extremity in instances in which the skilled use of closed reduction can be employed to avoid the calamities all too frequently associated with open reduction.

Fractures of the upper and middle third of the adult femur, the shafts of the radius and ulna, and olecranon in adults, to name a few, are stressed as lending themselves particularly well to primary open reduction, and in this view there would be few dissenters.

Charnley's thoughts in regard to plating tibial fractures and the relatively early delayed grafting of tibial shaft fractures ununited clinically at 3 months may not be accepted by some surgeons. Similarly, his acceptance of major fragment displacement in fractures of the posterior lip of the tibia in which the tibiotalar dislocation has been reduced will be challenged by many surgeons who believe that accurate replacement under direct vision, with adequate fixation, is essential for the prevention of late osteoarthritis of this joint.

Although this excellent treatise is intended primarily for house officers in the accident room, it would be well for each experienced surgeon to review the tenets set forth in the chapters on basic science and technique. They may provide a revelation to many who reflect on the courses to be adopted in the presence of difficult decisions to be made in fracture management.

Perhaps the most succinct summary of Charnley's philosophy is found on page 167 when he states that, "A good conservative method is one which yields a constant satisfactory result rather than a series of perfect cases interspersed with an odd catastrophe."

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

CIRUGIA GINECOLOGICA. By Dr. Oscar Blanchard. 593 pages, 507 illustrations. Buenos Aires, Argentina: Lopez Libreros Editores S. R. L., 1961.

SYSTEM OF OPHTHALMOLOGY. Edited by Sir Stewart Duke-Elder. Vol. II. THE ANATOMY OF THE VISUAL SYSTEM. By Sir Stewart Duke-Elder, G.C.V.O., F.R.S., and Kenneth C. Wybar, M.D., Ch.M., F.R.C.S. 901 pages, 842 illustrations. $30.00. St. Louis: The C. V. Mosby Co., 1961.

ACQUIRED DISEASE OF THE HEART AND GREAT VESSELS. By Jessee E. Edwards, M.D. Vol. I, Diseases of the Valves and Pericardium; Vol. II, Coronary Arterial Disease, Vol. III, Diseases of the Great Vessels. 1437 pages, 2333 illustrations. $70.00. Philadelphia and London: W. B. Saunders Co., 1961.

THORACIC DISEASES; EMPHASIZING CARDIOPULMONARY RELATIONSHIPS. By Eli H. Rubin, M.D., F.A.C.P., F.C.C.P., and Morris Rubin, M.D., F.A.C.S., F.C.C.P. With George C. Leiner, M.D., and Doris J. W. Escher, M.D. 968 pages, 461 illustrations. $25.00. Philadelphia and London: W. B. Saunders Co., 1961.

PROGRESS IN SURGERY. Progrés en Chirurgie. Fortschritte der Chirurgie. Edited by M. Allgöwer. Vol. I. 255 pages, illustrated. $15.00. S. Karger, 1961; New York: Hafner Publishing Co., Inc., exclusive U. S. agents.

THE NEWBORN CHILD. By David G. Vulliamy, M.D., M.R.C.P., D.C.H. 163 pages, 34 illustrations. $6.00. Boston: Little, Brown & Co., 1961.

WIEDERHERSTELLUNGSCHIRURGIE UND TRAUMATOLOGIE. Reconstruction Surgery and Traumatology. Chirurgie Réparatrice et Traumatologie. Annual Survey. Edited by M. Lange. Vol. VI. 139 pages, illustrated. $11.00. Basel and New York: S. Karger, 1961.

A MIRROR UP TO MEDICINE. By A. C. Corcoran, M.D. 506 pages, no illustrations. $5.75. Philadelphia and Montreal: J. B. Lippincott Co., 1961.

INJURIES AND INFECTIONS OF THE HAND. By Robert H. C. Robins, M.B., F.R.C.S. 220 pages, 157 illustrations. $13.00. Baltimore: The Williams & Wilkins Co., 1961.

OXYTOCIN; PROCEEDINGS OF AN INTERNATIONAL SYMPOSIUM HELD IN MONTEVIDEO, 1959. Edited by R. Caldeyro-Barcia and H. Heller. 443 pages, illustrated. $15.00. New York, Oxford, London, Paris: Pergamon Press, Symposium Publications Division, 1961.

A MANUAL OF PREGNANCY TESTING. By Edward H. Hon, M.D. 116 pages, 34 illustrations. $5.00. Boston: Little, Brown & Co., 1961.

FETAL ELECTROCARDIOGRAPHY AND ELECTROENCEPHALOGRAPHY. By Richard Lee Bernstine. 97 pages, 61 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1961.

PRINCIPLES AND PRACTICE OF SURGICAL NURSING. By D. F. Ellison Nash, F.R.C.S. 1032 pages, 385 illustrations. $7.00. London: Edward Arnold Publishers, Ltd., 1961; Baltimore: Williams & Wilkins Co., exclusive U. S. agents.

PATHOLOGY. Edited by W. A. Anderson, M.D., F.A.C.P. 4th ed. 1389 pages, 1385 illustrations. $18.00. St. Louis: C. V. Mosby Co., 1961.

SURGERY; PRINCIPLES AND PRACTICE. Edited by Henry Harkins, M.D., Carl A. Moyer, M.D., Jonathan E. Rhoads, M.D., and J. Garrot Allen, M.D. 2nd ed. 1595 pages, 652 illustrations. $17.00. Philadelphia and Montreal: J. B. Lippincott Co., 1961.

HISTOPATHOLOGIC EFFECTS OF LOCAL ANESTHETIC DRUGS AND RELATED SUBSTANCES. By Philip Pizzolato, M.D., and Walter Mannheimer, M.D. 100 pages, 42 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1961.

WILLIAMS OBSTETRICS. By Nicholson J. Eastman and Louis M. Hellman. 12th ed. 1230 pages. $16.00. New York: Appleton-Century-Crofts, Inc., 1961.

ANESTHESIA; A MANUAL FOR STUDENTS AND PHYSICIANS. By Stuart C. Cullen, M.D. 6th ed. 296 pages, 37 illustrations. $6.00. Chicago: Year Book Medical Publishers, 1961.

LA NEUMO-GINECOGRAFIA; SU VALOR Y UTILIDAD EN EL DIAGNOSTICO GINECOLOGICO. By Alfredo Diaz Bruzual. 110 pages, illustrated. Caracas: University Central de Venezuela, 1961.

NOVAK'S TEXTBOOK OF GYNECOLOGY. By Edmund R. Novak, M.D., and Georgeanna Seegar Jones, M.D. 6th ed. 842 pages, 580 illustrations. $15.00. Baltimore: Williams & Wilkins Co., 1961.

SOME ASPECTS OF OBLITERATIVE VASCULAR DISEASE OF THE LOWER LIMB. By J. A. Gillespie, M.D., Ch.M., F.R.C.S., and D. M. Douglas, Ch.M., F.R.C.S. 136 pages, illustrated. $7.00. Edinburgh and London: E. & S. Livingstone Ltd., 1961; Baltimore: Williams & Wilkins Co., exclusive U. S. agents.